November 1956 Vol. 6 No. 6

Ca

a Bulletin of

Cancer Progress

Published by the
American Cancer Society, Inc.

cytology— a new science?

Because of its practical usefulness in detecting cancer, "cytology" has come to mean to most doctors the examination of morphological features of individual, frequently isolated cells as contrasted with structural relationships presented by cells en masse. The term has acquired further limitations by being associated almost exclusively with the diagnosis of cancer. To be sure, both connotations are justified but "cytology" means much more than cellular anatomy and cancer detection.

In its modern, practical sense, cytology was first developed as a means of studying the endocrine physiology of the female sexual cycle, first in animals, then in women—leading soon to the identification of the estrogenic and progestational hormones. Then came its application to the discovery of cancer of the uterus and later of other sites yielding recoverable cells. But, valuable as this morphological aspect is, it may well prove to be the least of the advantages of cytology — the study of cells. For now are coming to hand the means of studying the cell's physiology. Such study already involves a number of pertinent approaches — qualitative and quantitative cellular chemistry, metabolism, protein synthesis, enzyme chemistry, physical chemistry, virology, and immune response, to cite a few.

It is one thing to be able to distinguish between the appearance of a cancer cell and a normal one. But it is something else — and of vastly more significance — to distinguish the behavior of the two, for, once that can be done, what makes them behave differently should not be far behind.

Cytology should not be regarded as just a new method of clinical diagnosis. It is a research sphere of first importance — a science in its own right.

Cover—

Mural bas-relief in the tomb of Ankh-ma-Hor, at Sakkara, reflecting the medical influence of its architect Imhotep, the Aesculapius of Egypt. This mausoleum is the most ancient of the pyramids (3000 B.C.) and the oldest structure now in existence.

The oldest known mummy, that of Ra-Nefter, formerly in the Royal College of Surgeons' Museum, presented evidence of preputiotomy, the early Egyptian variation of circumcision.

Circumcision and coital hygiene are important prophylactic measures against cancers of the penis and cervix. Cervical cancer has recently been induced in mice by the application of human smegma.

NEWSLETTER

NOVEMBER, 1956

The First International Cancer Cytology Congress, held in Chicago, October 8 to 12, constituted a recognition of the Papanicolaou technique as a major cancer-screening procedure. It was sponsored by the American Society of Clinical Pathologists, the College of American Pathologists, the Inter-Society Cytology Council, and the International Union Against Cancer.

Background: Papanicolaou (Cornell) was awarded a C.A.P. honorary fellowship, one of many honors bestowed upon him during the past five years of his distinguished career. His notable achievements, however, dated back thirty years, some of which were marked by the abuse of skeptical and cynical colleagues. At the Congress he traced the genesis of cancer cytology back to Donne in 1838, a contemporary of Schleiden and Schwann, and described the emergence of the cell theory. He cited Nathan's diagnosis in 1914 of a case of breast cancer from breast secretions and mentioned other early ventures before and after his own first publication in 1928 on vaginal smears. It was only after the widespread publication in lay journals that followed the 1947 International Cancer Congress in St. Louis that the medical profession as a whole became interested in the technique.

Papers at the Congress traced the rapid rise of the technique during the last decade to its present status as the most important mass screening device in existence. A few discussed cytology as a promising medium for the prognosis and treatment of cancer.

Today: Anderson (Miami) presented the results of a survey of C.A.P. members; 85 per cent of them last year did exfoliative cytology as part of their diagnostic work. Of them, 73 per cent were in private practice, 14 per cent in government work, 11 per cent in academic life, 10 per cent in hospitals, and 3 per cent in research; 1 per cent were residents, and for 1 per cent field was not stated. Of

course, some worked in two or more of these fields. The pathologists did cytodiagnostic work on various sites in these percentages: uterus 90, lung 91, stomach 62, other sites (including central nervous system) 74.

It appeared from these figures that cytodiagnosis was used in 1955 on 2,000,000 Americans. Anderson said that with present facilities, it could be used for an additional 2,200,000. For further expansion, the big need would be for trained technicians.

The taking of smears is relatively simple. The concensus was that any physician could take simple smears after brief training. This problem was much simpler than that of training technicians, who at this time usually are required to have two years of college science and six months of training in reading slides.

The training of pathologists to interpret smears also presented a problem. Some speakers contended that general proficiency in pathology does not by itself qualify one to interpret slides. Some proposed a minimum of three months of training in cytology for pathologists; others said they did all right after two weeks of intensive training and one year of self instruction in off-duty hours. Half of all the pathologists in the survey said they had had no formal training in cytodiagnosis. About 90 per cent had been doing cytodiagnosis for three years or longer.

Tomorrow: There were many indications that cytodiagnosis, though becoming increasingly popular, had not yet realized its potential.

Cameron (A.C.S.) asserted that "the problem of cervical cancer could be virtually eliminated if we could persuade all women to be examined by the cytology method at appropriate intervals -- tentatively once a year -- and if we had the professional manpower to interpret the slides." Admittedly they were two big if's -- there are thirty million women older than 40 years in the United States, and at present there are only 1230 pathologists who are "self-confessed cytologists." If an average screener can handle thirty slides a day, there would be a need for 3400 screeners, Cameron estimated. He said that a solution might come in the development of an automatic screening device; but Tolles's paper indicated that his automatic scanner, or cytoanalyzer, is far from perfected, and its success is problematical.

Heller (N.C.I.) urged all men older than 45 years

(Continued after page 220.)

CA
a Bulletin of Cancer Progress

NOVEMBER 1956 VOL. 6, NO. 6

CONTENTS

KEEPING UP WITH CANCER 182

AT A GLANCE 185

EXFOLIATIVE CYTOLOGY IN RESEARCH AND DIAGNOSIS
by George N. Papanicolaou, M.D. 190

WHAT IS CARCINOMA IN SITU?
by Arthur T. Hertig, M.D., and Hazel Mansell, M.B., B.S. 196

ENDOMETRIAL BIOPSY
by John C. Burch, M.D. 203

COLPOSCOPY AND THE DIAGNOSIS OF EARLY CARCINOMA OF THE UTERINE CERVIX
by Warren R. Lang, M.D. 205

CANCER CLINICS 208

NEW DEVELOPMENTS IN CANCER 214

AUTHOR INDEX 215

SUBJECT INDEX 217

Published bimonthly by

AMERICAN CANCER SOCIETY, INC.
New York, N. Y.

Annual Subscription $2.50

Special bulk rate to organizations other than Divisions subscribing in quantities of 200 or more.

Copyright©, 1956, by the American Cancer Society, Inc., New York, N. Y.

Cancer "Sword" Reg. U.S. Pat. Off.

Keeping up

Hormones, Radioisotopes, and Cancer

Gonadal steroid hormones give beneficial results in cancer of the breast and prostate. Adrenocorticotropic hormone and cortisone have limited beneficial effects in the lymphoma-leukemia group. Extirpation or inactivation of the ovaries, the adrenals, and the pituitary may alter the endocrine balance beneficially. Radioisotopes have limited specific usefulness and are generally combined with other therapeutic methods. In prostatic cancers the accepted regimen includes bilateral orchiectomy and estrogen (stilbestrol) therapy. Among the benefits of this therapy are immediate relief of bone pain, improvement in the sense of well-being and appetite, gain in weight, improvement in the anemia, and diminution in size of the primary and metastatic tumors. When androgen-suppression therapy eventually fails, further remissions of three to nine months may follow bilateral adrenalectomy. A still further short remission may result from reinstitution of estrogen therapy. Inoperable carcinoma of the breast should be treated with roentgen rays preliminary to steroid therapy. An artificially induced menopause should precede the use of androgens. Estrogens are used in women at least five years postmenopause. Objective regression follows these procedures in a third of the patients. Androgen therapy does not prolong life but it relieves pain and improves the sense of well-being. Hormones should not be used until the disease exacerbates. As yet there is insufficient evidence to allow critical evaluation of adrenalectomy in breast cancer. In cancer of the male breast castration may give a remission of three years, and stilbestrol is used when exacerbation occurs. ACTH and cortisone are useful in leukemia and the lymphomas. Remissions of two to nine months are noted in 70 per cent of children with acute leukemia treated with ACTH. Radium and four radioisotopes have been widely used in the treatment of malignant disease — I^{131}, P^{32}, Au^{198}, and Co^{60}. I^{131} is concentrated to effective levels in any malignant thyroid tissue retaining its ability to concentrate iodine. Effective therapeutic levels of I^{131} may be obtained by preliminary administration of thiouracil or propylthiouracil for a period of six to eight weeks. P^{32} is of value in treatment of polycythemia vera and in chronic myeloid and chronic lymphatic leukemia. Au^{198} is of greatest use in treating secreting serous membranes that are the result of malignant processes within the chest or abdomen. Au^{198} is also used in cancer of the prostate and prophylactically after surgery to combat the seeding of the pleural and peritoneal surfaces with tumor cells. Radium and Co^{60} applicators allow for placing large amounts of radiation into cavities for effective therapeutic exposures. They provide gamma rays equivalent to those from supervoltage roentgen-ray machines.

Brayer, F. T.; Glasser, S. R., and Howland, J. W.: Hormones and radioactivity in cancer therapy. New York State J. Med. 56:905-909, March 15, 1956.

Polyps, Ulcerative Colitis, and Cancer

A weighty argument in favor of ileostomy and colectomy in protracted, grave cases of colitis is the fact that carcinoma occurs in increased frequency in ulcerative colitis, that it occurs in cases of long

with Cancer

standing, and that it has a markedly severe prognosis. Inflammatory polypoid changes occur in approximately 65 per cent of severe cases of ulcerative colitis. The incidence of cancer in cases of ulcerative colitis of eight years' duration is stated to be 25 to 30 per cent. In the literature the incidence of cancer in ulcerative colitis ranges from 3.8 to 4.5 per cent, well above the incidence in the control population of the same age group. Practically all carcinomas of the colon occurring with, and in, ulcerative colitis are located in the rectum or the rectosigmoid. Many pathologists consider carcinoma arising in an area of polypoid colitis as unrelated to the colitis and as arising on the basis of an incidental adenomatous polyp, such as may be found in a large percentage of the control population, or on the basis of a familial colonic polyposis with superimposed ulcerative colitis.

Crohn, B. B.: Indications for ileostomy and colectomy in ulcerative colitis. New York State J. Med. 56:860-863, March 15, 1956.

Cancer and Sex

Analysis of the age-adjusted–incidence rates of cancers of nonsexual sites reported in New York State (excluding New York City) confirmed the well-known variation in the sex distribution of cancers of different sites and suggested the probability of environmental and/or endogenous factors predisposing to cancer of nonsexual sites in females. Cancers of the nonsexual sites, lip, larynx, tongue, lung, and bronchus, are more prevalent among males—masculine cancers. Cancers of the colon and stomach are about equally distributed between the two sexes—neutral cancers. Cancers of the thyroid and biliary passages are more common among females—feminine cancers. Female patients with masculine cancers had fewer pregnancies and more abortions than had the female patients with neutral cancers; and female patients with feminine cancers had fewer abortions than had the females with neutral cancers. These differences were interpreted as suggesting the existence of an endocrine factor in these cancers of nonsexual sites. When incidence of these three groups of cancers—masculine, neutral, and feminine—was correlated with age and sex, it was found that, in the masculine group of cancers, the male incidence increased at a greater rate than did the female rate during the early part of life and that, at about the time of the climacteric, the rate of increase in the female incidence paralleled or was greater than the male rate of increase. This is consistent with the feminization of men and the masculinization of women beyond the climacteric. No climacteric influence was noted on the incidence rates for the neutral cancers. In the feminine cancers the age-sex relationships were opposite in direction to those in the masculine cancers. The larynx is a secondary sex organ and has the same embryological anlage as the bronchus and lung. These data suggest an endocrine predisposition to cancers of some of the nonsexual sites.

Lilienfeld, A. M.: Possible existence of predisposing factors in the etiology of selected cancers of nonsexual sites in females; a preliminary inquiry. Cancer 9: 111-122, Jan.-Feb., 1956.

Treatment of Cancer

Little improvement can be expected in the treatment of cancer from the stand-

point of more radical operative procedures, for this field has been extended almost to the anatomical limit. However, there is opportunity for improvement in prophylactic measures, such as minimizing the spread of cancer during an operative procedure. An unsuccessful attempt to remove a cancer disseminates it and shortens the patient's life. Every possible method should be used to determine inoperability before the operation is started. Radical operative procedures with high mortality rates are not justified in certain tumors with low five-year–survival rates. The laity must be educated concerning dangerous symptoms and urged to seek medical aid and advice immediately. In most cancers the patient can be given a favorable prognosis if therapy is undertaken soon after development of manifestations. When the patient is seen too late for effective surgical or radiation therapy, palliative measures must be used. Among the psychological palliative measures is impressing the patient with the fact that spontaneous regressions are more frequent than formerly supposed, and that the more rare spontaneous cure is always possible in his case. More effort should be made to correlate examples of regression and of slow growth of tumors. The immunological phase of cancer research appears to be about as important as research in chemical therapy.

Cole, W. H.: Problems and obligations in the treatment of cancer. [Editorial.] Surgery 39:889-891, May, 1956.

Cancer of the Breast—Symptoms and Prognosis

In more than 80 per cent of all cases in the present material (1042 cases) the first symptom was a lump in the breast which sooner or later caused the patient to consult a doctor. In the remaining 20 per cent some other symptom was noted as the first sign of the disease. Half of these patients, however, waited to seek medical advice until they themselves found a tumor in the breast. Thus 90 per cent of all the patients in the writer's material sought medical advice on the grounds of a tumor and the other 10 per cent for other reasons.

Many patients noticed several symptoms that could later be associated with the disease. These symptoms were the following: 90 per cent noticed a tumor in the breast; 20 per cent had pains, usually described as an intermittent sticking or quivering sensation; 18 per cent noticed retraction of the nipple; 9 per cent had discharge from the nipple—sanguineous in somewhat more than half the cases; 6 per cent noticed swollen lymph nodes in the axilla; 3 per cent noticed eczema on or around the nipple; 3 per cent noticed deterioration of their general condition.

In assessing the value of various therapeutic methods in inoperable cancer of the breast, consideration must also be paid to the course of the disease when no treatment is given. The following table compares the length of survival in nearly 800 untreated patients with cancer of the breast, calculated from the onset of the first symptoms, with the length of survival in a series of more than a thousand patients treated at Radiumhemmet, Stockholm.

Percentage of Survivals

Years	1	2	3	4	5	6	7	8	9	10
Untreated	59	37	24	17	13					
Treated	82	64	52	45	40	35	32	32	29	27

[These figures contradict the experience of Hippocrates that "it is better to omit treatment altogether; for if treated, the patients soon die, whereas if let alone, they may last a long time."—Ed.]

Nohrman, B. A.: Cancer of the breast; a clinical study of 1042 cases treated at Radiumhemmet, 1936-1941. Acta radiol. Suppl. 77: 5-98, 1949.

a glance . . .

one-minute abstracts of the current literature on cancer . . .

Cytological Diagnosis of Cervical Cancer

Cytological screening is of distinct value in detecting early invasive carcinoma of the cervix in the preclinical stage, as well as carcinoma in situ. Ten of eighteen cases of carcinoma of the cervix found in a group of 4200 patients screened by cervical exfoliative cytological technique were in the invasive stage; the other eight had carcinoma in situ. In all eighteen the clinical impression was other than carcinoma, the first positive indication being the result of cytological examination. The entire group of 4200 patients were seen in a clinic-type practice. Among the clinical impressions at the time of the smear were: cervical erosion, chronic cervicitis, hypertrophic cervicitis, and bullous cervicitis. Three of the ten cases of invasive carcinoma had no clinical lesion of the cervix. In order to compare results of cervical cytological technique in clinic and private practices, 1000 consecutive privately referred patients were studied. Six carcinomas of the cervix were detected, all clinically unsuspected. Of these six, three were invasive. These results suggest that a comparable percentage of early invasive carcinomas of the cervix will be detected in private and clinic practice. In another series of 740 cases of clinical invasive carcinoma of the cervix, there were thirteen cases in which previous cervical biopsies had been performed, and in twelve of these the biopsy diagnosis had been carcinoma in situ. Carcinoma in situ is coming to be regarded as actually true carcinoma in a preinvasive stage. On the other hand one investigator, following forty-one women with untreated carcinoma in situ for ten years, found but one patient who developed invasive carcinoma. There is general agreement that early diagnosis and treatment of invasive cancer of the cervix are of paramount importance and that detection in the preclinical stage is highly desirable. There is much evidence that cytological screening is an important means to these ends.

Wrobel, C. J.: Detection of invasive cervical cancer by exfoliative cytology. Am. J. Obst. & Gynec. 71: 402-406, Feb., 1956.

Cancer of the Cervix—Treatment

In stage O, panhysterectomy with excision of a 2-cm. cuff of parametrium and vagina is the treatment of choice, and yields practically 100 per cent cures. In stage I, irradiation with roentgen rays and radium is to be preferred, and radical hysterectomy yields its best results in this stage. Reports of a large series of cases show 64.4 per cent cure rate from radia-

tion and 60.1 per cent from surgery in this stage. In stage 2, radiation is much to be preferred to radical hysterectomy. For stages 3 and 4 there is no satisfactory treatment, but the best curative and palliative therapy is radiation. Exenteration is not generally justified as the pain and annoyance of the operation is often added to that of the persistent carcinoma. In radioresistant lesions of stage 1 or 2, radical hysterectomy may be indicated. Carcinoma of the cervical stump is usually best treated by radiation. Generally, the best treatment for carcinoma of the cervix is the same with as without pregnancy. Delay in treatment until after delivery may be indicated. About one half of patients given definitive treatment will remain uncured. These patients must be kept in the best possible general physical condition and given supportive medication, analgesics, and narcotics as indicated.

Loomis, R. O.; Prioletti, M.; Berne, A. S., and Clark, C. E.: The treatment of carcinoma of the cervix. New York State J. Med. 55:3480-3484, Dec. 1, 1955.

Endometrial Cancer

The former ratio of fundal to cervical cancers of 1:8 has changed in the past few years to nearly 1:1, indicating the necessity for greater emphasis than has formerly been given to the management of endometrial cancer. Best reported survival rates have been obtained in fundal cancer from the use of preoperative irradiation from intrauterine radium and bilateral salpingo-oophorectomy in six to eight weeks. The most commonly used source of radium is the tandem of 50- or 100-mg. capsules, inserted at the time of dilatation and curettage for diagnosis. Insertion of radium into the uterine cavity is grossly inaccurate in placement and distribution. Surgery alone gives the lowest recurrence rate. Roentgen rays and radium therapy alone gave poor results. Those cases presumably cured by this method were superficial lesions of low malignancy of polypoid type in which the curettage was largely responsible for eradication of the tumor. A more extensive operation than usual, including pelvic lymphadenectomy, is described; with it the author hopes to reduce the recurrence rate in patients whose disease extends beyond the uterus.

Sadler, J. M.: Problems associated with treatment of cancer of the endometrium. Am. J. Obst. & Gynec. 70:17-28, July, 1955.

Cytological Diagnosis of Uterine Cancer

As a routine office procedure by the staff of the Milwaukee Hospital during the past five years, cervical scrapings from 7577 patients were examined cytologically. Abnormalities were shown in 585 (8 per cent). Of these, eighty-two patients were found to have histologically proved carcinoma—usually early and asymptomatic. Since smear examination is a screening method rather than an absolute diagnostic procedure, the false positives encountered are no drawback for each positive smear is confirmed by biopsy before treatment is begun. Five false negatives were obtained, four attributable to the examiner's lack of experience and one in a patient with ulcerating carcinoma that could not have been overlooked. The smear proved valueless in this series for the diagnosis of endometrial cancer. Endometrial curettings in 1685 patients disclosed endometrial carcinoma in twelve patients without, and seven patients with, symptoms. Cytological methods yield best results when applied routinely in every pelvic examination. The greatest use of the smear is for the diagnosis of early, asymptomatic cervical carcinoma.

Birge, E. A., and Carlson, D. J.: Experience with cytology in diagnosis of uterine carcinoma in a private hospital. Am. J. Clin. Path. 26:277-282, March, 1956.

Postoperative Irradiation in Ovarian Cancer

In malignant tumors of the ovary the surgery of choice is bilateral salpingo-oophorectomy with total hysterectomy. In a series of ninety-six proved cases of carcinoma of the ovary, sixty-four, mostly in stage 1, were treated by surgery alone,

with 22 per cent surviving at the end of five years, and thirty-two, mostly in stage 3, by surgery and postoperative radiation with 53 per cent five-year survival. Postoperative irradiation, in adequate dosage, definitely increases the survival rate of patients in whom the tumor cannot be completely excised. When first diagnosed, the majority of patients have extensive intra-abdominal metastases that cannot be completely removed. The insidious onset and rapid spread through the abdominal cavity by implantation gives rise to no early alarming symptoms. Later the commonest symptoms are abdominal swelling and pain, gastrointestinal and genitourinary complaints, backache, weight loss, and menstrual irregularity. The physician should make frequent and accurate pelvic examinations and should educate his patients, especially those past the menopause, as to the early symptoms and signs of this condition. About 4 per cent of all malignant tumors in women are of the ovary. About 15 per cent of all ovarian tumors are malignant, and approximately one half of these are bilateral.

Gardiner, G. A., and Slate, J.: Malignant tumors of the ovary. Am. J. Obst. & Gynec. 70:554-562, Sept., 1955.

Endometrial Aspiration Smear

A simple, inexpensive, and painless technique for the endometrial aspiration smear is described and recommended as a practical office procedure for preliminary investigation of abnormal uterine bleeding. Because vaginal smears often fail to yield material for a diagnosis of carcinoma of the endometrium, this procedure is recommended for women with metrorrhagia, menorrhagia, menometrorrhagia, and postmenopausal bleeding. Diagnoses are reported only as positive, negative, or suspicious but negative. Hyperchromatism, variation in size and shape of the nucleus, and irregularity of the chromatin network are significant for a diagnosis of malignant growth. With adenocarcinoma of the endometrium, the malignant cells are granular and generally smaller than squamous cells of the cervix. The cells may or may not be differentiated depending upon the definition of cellular borders. Undifferentiated adenocarcinoma cells appear in tight groups with indistinct cellular borders. Vacuolization of the cytoplasm is less pronounced than in differentiated cells. Clusters of normal endometrial cells are generally found with malignant cells in positive smears. When aspiration smears are positive, curettage or operation is performed, and the tissue is examined. Occasionally, aspiration smears will show adenocarcinoma when curetted material does not. Even the most meticulous exploration may fail to reach some of the less accessible endometrial areas, such as the cornual regions, the apex of the fundus, and low on the anterior wall just inside the internal os. Cancer cells, being less cohesive than normal cells, are more readily exfoliated and tend to appear in abundance on cytological smears. This technique is carried out by painting the cervix and endocervical canal with an antiseptic solution, and introducing a malleable Killian antrum cannula, 2 mm. thick, into the endometrial cavity. If any difficulty arises in passing the internal os, a tenaculum is placed on the anterior lip of the cervix. When the cannula is in the uterus, a 5- or 10-cc. syringe is attached and gentle suction applied. The cannula is then removed and the aspirated material is expressed on a clean, dry slide and immediately immersed in fixative. The smear should be thin. Only one or two drops are placed on the slide and spread like blood smears with a second glass slide. The nucleus is stained with Harris's hematoxylin; the cytoplasm is counterstained with OG6 and EA36 or EA50.

Hecht, E. L.: The endometrial aspiration smear; research status and clinical value. Am. J. Obst. & Gynec. 71:819-831; disc. 832-833, April, 1956.

Unsuspected Uterine Cancer

In a series of 1000 hysterectomies performed for benign gynecological conditions—excluding all hysterectomies as a planned part of an operation for carcinoma, cesarean hysterectomies, and

those indicated for obstetrical reasons or complications—the pathological findings disclosed five cases of cervical carcinoma in situ, seven cases of invasive carcinoma of the cervix, and three cases of endometrial carcinoma. Only 34.7 per cent of the 1000 patients had had preoperative curettage, biopsy, or vaginal smears. All patients who are to undergo hysterectomy should have the benefit of one or more of these diagnostic tests.

Watts, W. F., and Kimbrough, R. A., Jr.: Hysterectomy; analysis of 1000 consecutive operations. Obst. & Gynec. 7:483-493, May, 1956.

Carcinoma of the Corpus Uteri

Survey of the cases of carcinoma of the uterus at Reading (Pa.) Hospital from 1936 to 1949 included 105 patients with carcinoma of the endometrium, yielding a ratio of endometrial to cervical carcinoma of 1 to 1.6. The most frequent presenting symptom was abnormal vaginal bleeding. Radiotherapy had been given for previous benign lesions in 7.6 per cent of the patients. Fibromyomas were present in 46 per cent, and endometrial hyperplasia, prior or present, in 22 per cent. A diabetic trend was found in 17 per cent and obesity in 79 per cent. Five-year–survival rates resulted from treatment as follows: 64.5 per cent from hysterectomy with bilateral salpingo-oophorectomy; 83.3 per cent from intracavitary radium followed by total hysterectomy; and 69.2 per cent from radium and roentgen rays or from radium alone.

Nugent, F. B., and Gleichert, J. E.: Carcinoma of the endometrium; survey of treatment and end results in a community hospital. Obst. & Gynec. 7:406-411, April, 1956.

Cervical Cancer in Situ

One hundred eighteen cases of carcinoma in situ of the uterine cervix are reported. The diagnosis of this condition is dependent upon histopathological examination and the problem of the clinician is to obtain representative specimens. Experience with this review indicates the need for conventional punch biopsies at the squamocolumnar junction and for curettement of the endocervical canal before assuming the lesion to be entirely intraepithelial. Vaginal cytology is invaluable in detecting carcinoma in situ, but a positive report must be confirmed histologically. Of seventy-five patients who had vaginal smears prior to therapy, sixty-eight (90 per cent) had positive smears. Therapy of this group was almost entirely surgical. Total hysterectomy was done in ninety-four instances. In the absence of characteristic symptoms or physical findings in carcinoma in situ, diagnosis cannot be made from history and physical examination but must depend upon the histopathological examination. The minimum of procedures before accepting a lesion as carcinoma in situ, or to exclude it after a positive smear report, is a four-point biopsy of the squamocolumnar junction and an endocervical curettage. The Schiller test can be of added value, since the area of carcinoma in situ, containing no glycogen, will not stain with iodine.

Fennell, R. H., Jr.: Carcinoma in situ of the uterine cervix; a report of 118 cases. Cancer 9:374-384, March-April, 1956.

Cervical Cancer and Social Conditions

In the forty-eight County Boroughs of England and Wales having populations of more than 100,000, in the three years 1950 to 1952, there were 2257 deaths attributed to cancer of the cervix. The death rates from cervical cancer in these boroughs were much higher for childless married women than for single women, and rates at ages less than 65 were particularly high among wives of unskilled laborers. Early marriage was found to be a more important factor than the number of confinements, confirming Wynder's study of American women. Seaports and textile towns have high rates for cervical cancer. There appears to be some special factor increasing the risk of cervical cancer, as is the case with skin cancer, among women who work in textile mills. And the social conditions in seaports or some specific factor of mercantile occupations of men increases the risk of cervical cancer among the female population. Mortality

rates from cervical cancer were high among populations of predominantly lower social classes and where the densities of persons per room was great. Risk of cervical carcinoma is a function of the total amount of sexual intercourse, pregnancies contributing little or nothing when marriage occurs early.

Stocks, P.: Cancer of the uterine cervix and social conditions. Brit. J. Cancer 9:487-494, Dec., 1955.

Cytological Diagnosis of Uterine Cancer

Papanicolaou first applied the study of exfoliated cells to the diagnosis of uterine cancer in 1923. To the original vaginal-smear method were added techniques for endocervical and endometrial smears. Cancer cells have less adherence than cells of normal tissues and desquamate constantly from all free surfaces, even from carcinoma in situ of the cervix. These exfoliated cancer cells have definite and characteristic morphological differences from normal cells, easily recognized by the expert cytologist. These cancer cells appear long before symptoms, affording a method for early detection and screening. In Memphis and Shelby County, Tennessee, 70,000 women were screened by the cytological method. Positive or suspicious smears were found in 1.9 per cent. Biopsies, completed in 81 per cent (1076) of these cases showed 527 cancers of the uterus of which 254 were early invasive and 282 were intraepithelial or noninvasive. Cancer of the cervix may exist for varying periods of time in a noninvasive form that is 100 per cent curable. The cytological test is a practical, efficient means of detecting early uterine cancer.

Kaiser, R. F.: Cytology as an aid to the diagnosis of uterine cancer. GP 13:83-84, April, 1956.

Cervical Cancer Accidentally Discovered

During the thirty years prior to 1952, at the Rhode Island Hospital Tumor Clinic, 1168 patients were seen. Of these, 251 (21.4 per cent) had cervical carcinoma. In twenty-seven (11 per cent) of these 251 cases, no consideration of cervical cancer was entertained prior to operation for other indications—cervicitis, fibroids, adnexal pathology, and prolapse—and the carcinoma was discovered at operation or afterward, histologically. Now that total hysterectomy is almost everywhere replacing the subtotal operation, accidentally encountered cervical cancers will be found more frequently, and the incidence of cancer of the cervical stump will decrease. After the initial treatment and subsequent surprise report from the pathological laboratory, various methods of treatment were employed according to the individual indications—selective radium treatment for local recurrences, roentgen-ray therapy, and retroperitoneal node dissection. The majority of cases of unsuspected cervical cancer are asymptomatic; a determined effort should be made to arrive at a proper diagnosis preoperatively. Survival results are proportional to the stage of the disease.

McDuff, H. C., Jr.; Martin, R. E., and Waterman, G. W.: Accidentally encountered cervical cancer. Am. J. Obst. & Gynec. 71:407-412, Feb., 1956.

Topography of Cervical Carcinoma

Histological study of the entire cervix was made in eighty-three cases of carcinoma. The lesion was found on the exocervical side of the external os in two, on the endocervical side in forty-two, on both sides in eleven, and was not determinable in twenty-eight. In two cases the carcinoma was found on the squamous side of the squamocolumnar junction, in thirty-five on the columnar side, in three on both sides, and was not determinable in forty-three. Thus it is seen that about one half of cervical carcinomas in their early phases are missed when the physician's examination is limited to inspection and palpation. Examination of endocervical smears or of curettings from the endocervical canal is essential to avoid overlooking at least one half of early cancers.

Marsh, M.: Original site of cervical carcinoma; topographical relationship of carcinoma of the cervix to the external os and to the squamocolumnar junction. Obst. & Gynec. 7:444-452, April, 1956.

Exfoliative Cytology in Research and Diagnosis*

George N. Papanicolaou, M.D.

As the science of morphology moves forward, interest is centered more and more on what is to be considered as the basic structural unit of all living organisms, the cell. Cytology is thus destined to assume an increasingly significant role in biological and medical research. A cell, though closely integrated with other cells in the formation of a larger functional unit, still retains its individuality and has its own life history. Each cell performs its predestined function and passes away to leave its place to a new cell.

One cannot help but admire the wonderfully balanced mechanism of this ceaseless process of death and regeneration, which actually constitutes a continuous rejuvenation of the body and forms the physical basis of our ever-renewing personality.

This fundamental biological law finds a most typical expression in the epithelial tissues, i.e., the skin, which forms a protective sheath over our body, and the mucous membranes, which line all body cavities. These tissues, because of their exposure to the action of extraneous factors, are subjected to an extensive shedding of their superficially located cells. As these cells are lost, their places are promptly taken by new cells growing from the undifferentiated basal layer of the epithelium, which is endowed with an inherent high potentiality for proliferation and growth.

Epithelial cells exfoliating within the cavities of various organs, such as the vagina, uterus, lung, esophagus, stomach, sigmoid colon, urinary bladder, and others, may be detected and studied microscopically in properly fixed and stained smears prepared from fluid aspirated from these cavities. If the smears are fixed immediately, the cells, though they may be dead or partially degenerated, retain their structural characteristics to a degree permitting identification as to their origin and type.

The microscopic study of these exfoliated cells, which are actually waste epithelial elements, has grown to such an extent in the past few years as to reach the status of an autonomous branch of the cytological sciences, known under the recently coined term "Exfoliative Cytology." Its general significance has been greatly enhanced by its useful application in the diagnosis of malignant disease.

It so happens that all malignant neoplasms known as carcinomas have their inception within the epithelial lining of the various organs of the body and, as such, are subjected to the same fundamental biological laws that govern the proliferation, growth, and exfoliation processes peculiar to the epithelial tissues. Thus a carcinoma developing within the surface epithelium of an organ continuously throws off some of its superficial cells. Should this be a carinoma of the uterine cervix, no matter how small, even if it were so small as to be invisible to the naked eye, it would shed some of its superficial cells into the cervical canal. This shedding might occur at a rate far exceeding that of the normal cervical epithelium, since cancer cells are known to multiply and grow much faster than their normal counterparts. By examining microscopically a smear prepared from fluid aspirated from the vagina or the cer-

*Read at the presentation of the Passano Award in Chicago on June 13, 1956.

The investigative work referred to in this paper was aided by grants from the Commonwealth Fund and the American Cancer Society, Inc.

vical canal, one would thus be able to detect cells exfoliated from a cancerous area and identify them with the aid of morphologic criteria, by which their malignant nature can be ascertained. As a result, a carcinoma of the uterine cervix can be diagnosed by the smear method at a very early stage, prior to invasion and to the appearance of any symptoms. At this stage, cancer is still a localized lesion and can be removed by surgery or destroyed by irradiation with very good chances for a complete cure.

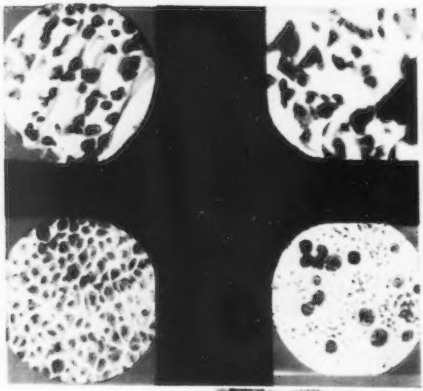
Before going further into the discussion of the usefulness of the cytological method in diagnosing cancer of other organs, it might be of interest to go back some forty years to the time when the vaginal-smear technique was introduced in our laboratory. In those days the problem with which the late Charles R. Stockard and I were concerned was of a basic morphological nature and had no relation to cancer. The development of the vaginal-smear technique was not the major objective of our investigative plans. It was devised simply as a means of determining the time of ovulation in the guinea pig in order to obtain adequate ovarian material for the study of the sex chromosomes in the maturing ovum. In those early days no one could foresee that this simple technique would become such a valuable tool in biological research and later in clinical diagnosis. It was indeed a thrilling experience to observe for the first time the striking morphological changes appearing in the vaginal smears of guinea pigs during the successive stages of each sex cycle. A simple test was thus brought to light that made possible the accurate evaluation of the time of ovulation and a better correlation of the morphological and physiological changes occurring periodically in the reproductive organs of the guinea pig.

Figure 1 shows four distinct cytological patterns appearing in sequence in the vaginal smears of a guinea pig. Each pattern typifies a different stage of the estrous cycle and, therefore, a different functional state in the organs of the female genital tract. The change from the upper left to the upper right indicates the peak of follicular activity. The cells of the two lower patterns are from the deeper layers of the epithelium and mark the completion of the ovulatory process.

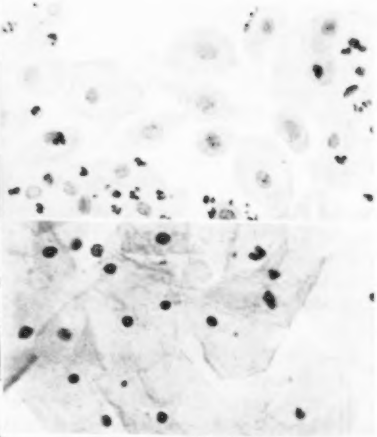
The application of this relatively simple cytological procedure opened a broad avenue of biological research, since it proved to be particularly suitable for the study of the female reproductive functions and their cyclic expression in both lower and higher mammals and ultimately in women. Brilliant studies by many investigators, Allen and Doisy, Evans, Corner, Hartman and others, threw new light on the correlation of ovarian and uterine morphological and physiological changes during the various phases of the normal sex cycle and their dependence upon the hypophyseal and other hormonal secretions. This marked the first significant branching of the tree of exfoliative cytology, which initiated a period of intense investigative activity in morphology, physiology, biochemistry, and even in experimental psychology. The estrogenic hormone, a sex hormone produced primarily within the ovarian follicles, was isolated with the aid of the vaginal smear. To change completely the vaginal-smear cytology of a postmenopausal woman to that characteristic of a young, normally menstruating woman by the administration of an estrogenic preparation was an exciting achievement. It also proved to be fruitful, since this inducible alteration in vaginal-smear cytology was later employed as an objective test for assaying estrogenic preparations and evaluating their physiological and therapeutic action in women. This test, which is still widely used, was developed in co-operation with the late Ephraim Shorr of our Department of Medicine.

The upper half of Fig. 2 shows a postmenopausal-smear pattern from a 58-year-old woman. The lower half illustrates a smear from the same woman after treatment with an estrogen.

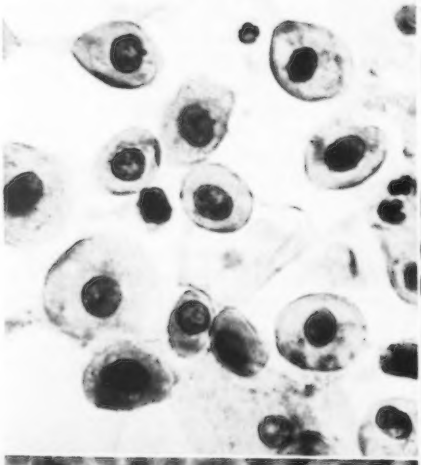
The possibilities of using the vaginal smear in the diagnosis of uterine cancer became apparent as far back as 1923, during the course of an exploratory project, carried out in co-operation with the Woman's Hospital of New York City. This



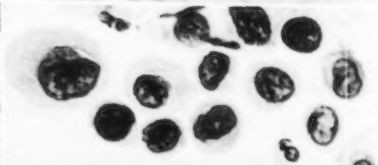
1

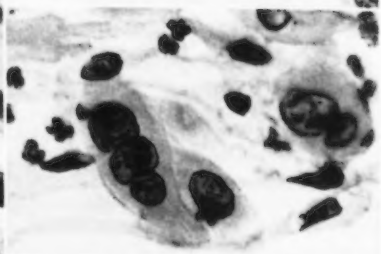


2

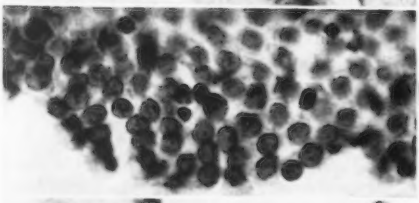


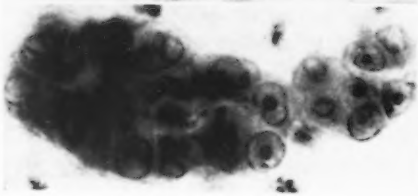
3



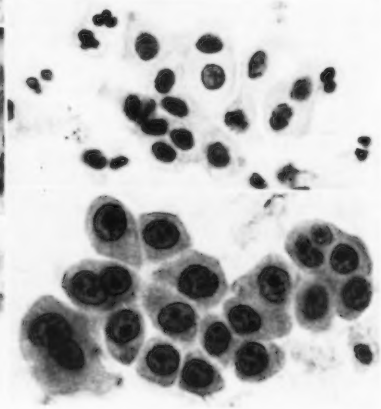


4





5



6

project was a study of the cytology of the vaginal secretion, first in normal women and then in patients with various pathological conditions of the uterus, including benign and malignant neoplasms. It was soon realized that malignant cells exfoliated from a carcinoma of the cervix could be fairly accurately differentiated from nonmalignant cells by their striking structural abnormalities. The enlargement and deep staining, so-called hyperchromasia, of the nuclei of the malignant cells cause them to be particularly conspicuous. One is bound to be much impressed, and, I may say, somewhat excited by looking at such cells for the first time.

Figure 3 illustrates normal cervical cells from a postmenopausal woman. The nuclei are uniform in size and show no hyperchromasia. The magnification in this slide is the same as that used in all the following slides.

Figure 4 shows malignant cells from two carcinomas of the cervix. The cells in the upper half of the slide are from a case of an early intraepithelial carcinoma, while those of the lower half are from a carcinoma of the cervix at an advanced invasive stage. Note the irregularity and deep staining or hyperchromasia of the nuclei. The cells of the advanced case show more atypical and bizarre forms.

Figure 5 shows one cluster of normal endometrial cells (upper half) and a cluster of malignant cells from a case of adenocarcinoma of the endometrium (lower half). The cells from intrauterine carcinomas are somewhat smaller and not so strikingly abnormal as those of the carcinomas of the cervix. However, their malignant nature is apparent when compared with corresponding normal cells, as in this slide.

The usefulness of the vaginal smear in the diagnosis of cancer of the uterus was first reported in 1928 in a preliminary note. However, it was not until 1943, with the publication of more extensive data in a monograph by Herbert Traut and me, that the method began to receive serious attention and to be tested in other laboratories.

Since 1945, the cytological method has been applied at a steadily increasing rate in the diagnosis of cancer of the uterus as well as in cancer of many other organs of the body. Its use has thus far been more effective in the diagnosis of cancer of the lung, urinary bladder, esophagus, stomach, rectum and sigmoid colon, and the pleural and peritoneal fluids. In all these organs, particularly in the lung, extensive tests have proved it to be an extremely valuable adjunct to biopsy and other established procedures for the diagnosis of cancer. Many unsuspected carcinomas have been detected by this method, some at a very early stage.

Figure 6 shows nonmalignant (upper) and malignant (lower) cells found in sputum specimens. The cells in the lower half are from a case of carcinoma of the lung.

Figure 7 shows normal and malignant cells found in urine-sediment smears. The cell clusters in the lower half are from a case of carcinoma of the bladder.

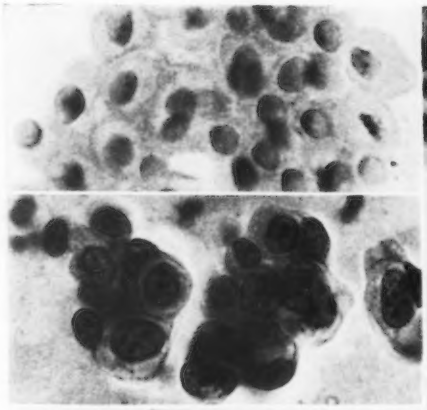
Figure 8 illustrates normal and malignant cells found in specimens of fluid aspirated from the stomach. The cells in the lower half are from a case of adenocarcinoma of the stomach.

Figure 9 shows nonmalignant and malignant cells found in rectal-washing specimens. The cells in the lower half are from a case of adenocarcinoma of the rectum.

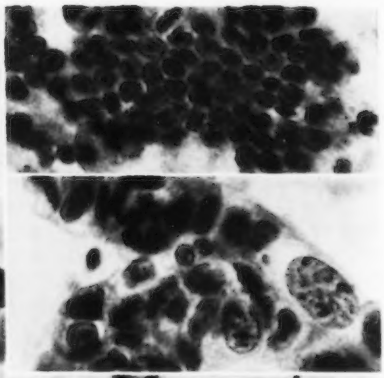
In some of the other organs, such as the prostate, the kidney, and the breast, the difficulty of obtaining adequate material has greatly handicapped the wider use of the cytological technique. However, even in these organs, cancer has first been diagnosed in many instances, and often at a very early stage, by cytology. In the breast, several cases of carcinoma have been uncovered by the microscopic examination of nipple secretion, even before the appearance of any palpable mass in the breast or any lymph-node involvement.

Figure 10 illustrates normal and malignant cells of a corresponding type found in urine-sediment smears. The cells in the lower half are from a case of carcinoma of the prostate.

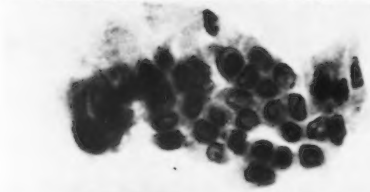
Figure 12, below, shows normal and malignant cells of a corresponding type



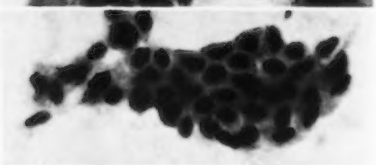
7



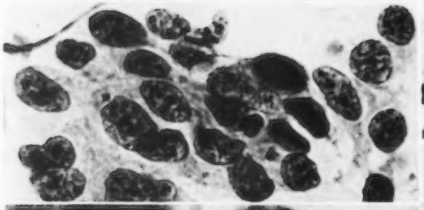
8

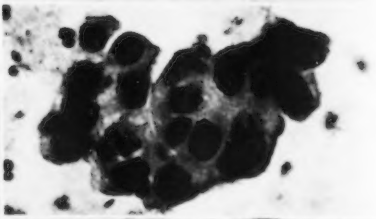


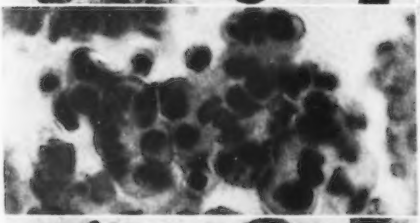
9



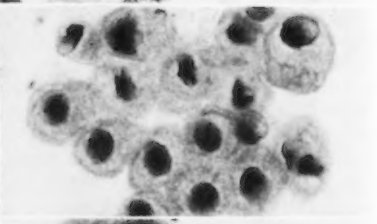
10



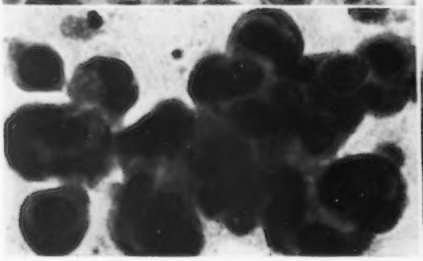


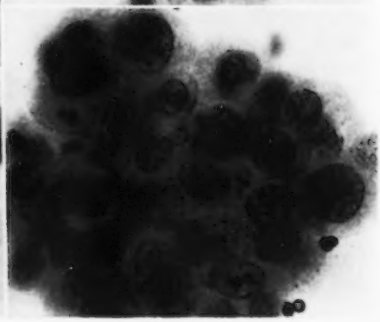


11



12





found in sediment smears from urine aspirated from the pelvis of the kidney. The malignant nature of the cells in the lower half is apparent. They are from a case of a very early preinvasive carcinoma of the pelvis of the kidney, first diagnosed by the cytological examination of the smears.

The cell clusters illustrated in Figure 11 were found in nipple-secretion smears. The one in the upper half is from a case diagnosed as benign papilloma of the breast. The one in the lower half is from a case of very early preinvasive carcinoma of the breast first diagnosed by the examination of the smears. This is one of several cases that have proved the feasibility of a cytological diagnosis of carcinoma of the breast at a very early stage, prior to the appearance of a palpable tumor.

All these applications in the diagnosis of cancer of various organs represent branches of what may be considered the second major, and perhaps the most vigorous, offshoot of the tree of Exfoliative Cytology. Its remarkable growth potentiality is evidenced by the rapidly spreading use of the method in cancer diagnostic centers all over the world and also by the enormous increase in the number of original articles and publications dealing with the subject of cytodiagnosis of cancer.

The cytological method has also proved to be a very valuable tool in cancer research. Its distinct advantage over other methods is that it makes possible a day-by-day follow-up, without surgical intervention, of the progressive as well as the regressive morphological changes occurring in spontaneous or experimentally induced malignant tumors. Furthermore, it permits an evaluation of the results of operative procedures and of the action and effects of various modes of treatment, including radiation, in experimental and clinical studies.

The cytological detection of numerous borderline or early malignant intraepithelial lesions of the uterine cervix in women has provided ample material for the study of the exfoliative cytology and histopathology of early cancer. There is hardly a problem related to cancer that currently absorbs the combined interest of pathologists, cytologists, and clinicians to a greater extent than that of carcinoma in situ of the cervix. A concerted attack has thus been launched on this problem. As a result, many fundamental facts have been disclosed that have thrown new light on the morphological, physiological, and histochemical changes preceding the appearance of frank cancer. The cytological method is thus particularly valuable in uncovering such morphological changes that may still be considered of precancerous or subcancerous nature.

Looking into the future one may anticipate further advances in our knowledge of cell morphology and the introduction of improved technical procedures, which may lead to wider utilization of the cytological method as a cancer-control measure. Pilot screening tests on large segments of the population under the auspices of the Public Health Service and the American Cancer Society have proved the practicality of mass screening for the purpose of detecting covert and asymptomatic carcinomas of the cervix.

However, one should not lose sight of the fact that the cytological method, which has met with universal favor within the past few years because of its successful application in cancer detection and diagnosis, is an outgrowth of fundamental biological studies. In this we may find the elements of another noteworthy example of the all-important role of basic research in opening new and ever-widening avenues of investigation leading to accomplishments of broad significance for the advancement of science and the benefit of mankind.

What is Carcinoma in Situ?

Arthur T. Hertig, M.D., and Hazel Mansell, M.B., B.S.

Carcinoma in situ is an apparently contradictory term. Carcinoma itself implies that invasion of stroma has already occurred, while "in situ" negates this interpretation. The term applied to the cervix uteri has been adopted by pathologists and gynecologists to mean the presence of morphologically malignant, but noninvasive, squamous epithelium involving the surface or both the surface and the gland lumina but without stromal invasion.

This condition has been described in the literature under a variety of synonyms; namely, incipient carcinoma, noninvasive potential carcinoma, preinvasive carcinoma, intramucosal carcinoma, Bowen's disease of the cervix, superficial noninvasive intraepithelial carcinoma, intraepithelial carcinoma, and precancerous anaplasia.

It is important to realize that a diagnosis of carcinoma in situ on a single cervical biopsy means only that carcinoma in situ is present in that biopsy material. It does not indicate what is present elsewhere in the cervix. UNTIL THE CERVIX HAS BEEN ADEQUATELY EXAMINED BY AT LEAST A SECOND SET OF MULTIPLE BIOPSIES AND A COINCIDENTAL ENDOCERVICAL CURETTAGE TO RULE OUT INVASIVE CANCER, THE MICROSCOPIC DIAGNOSIS OF CARCINOMA IN SITU SHOULD MEAN TO BOTH THE CLINICIAN AND PATHOLOGIST THAT THE PATIENT MAY WELL HAVE INVASIVE CERVICAL CANCER.

The uterine cervix harboring squamous-cell carcinoma in situ has no distinctive gross features other than the frequently present lacerations incident to delivery, with associated eversion, erosion, and chronic inflammation. The cervix may occasionally, however, appear completely normal or show a congenital erosion or leukoplakia (white areas of keratosis or parakeratosis). Commonest associated

From the Pathology departments, Free Hospital for Women, Brookline, and the Harvard Medical School, Boston, Massachusetts.

FIGURE 1. A low-power photomicrograph of the cervix uteri showing the distribution of squamous-cell carcinoma in situ. This may be readily distinguished from the normal squamous epithelium on the right because it stains more deeply owing to the nuclear hyperchromatism of the malignant cells. The carcinoma in situ extends from the region of the external os into the endocervix and is growing into and largely filling the endocervical glands. Everywhere it is well defined and does not go beyond limits of the endocervical glands. AFIP Acc. 573586-53-8358. (×9.2.)

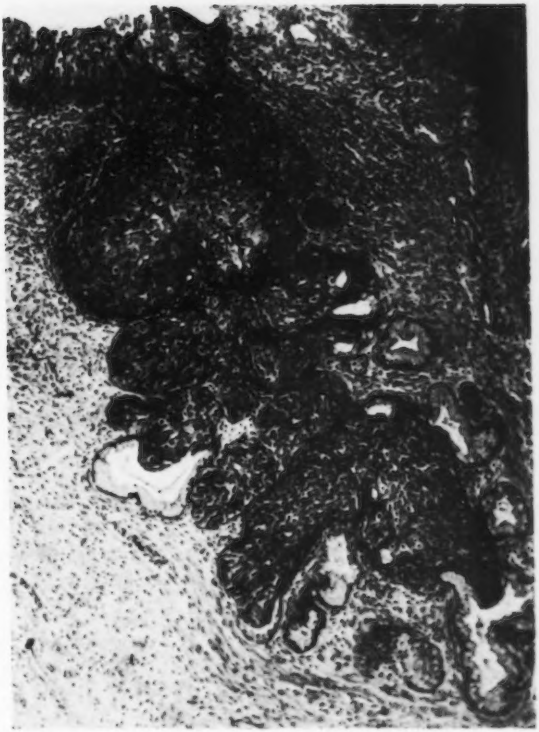


FIGURE 2. Squamous-cell carcinoma in situ of the cervix involving both surface and glands. The malignant epithelium has extended into this gland distorting it greatly but without invading the adjacent cervical stroma. Even at this magnification cellular pleomorphism may be noted. See Fig. 3 for details. AFIP Acc. 321804. (×55.)

finding is an erosion (79.3 per cent of cases). The cervix may or may not bleed easily when touched with a cotton swab. In order to determine the presence of benign or malignant non–glycogen-containing epithelium, the Schiller test should be applied to the cervix. The latter should be carefully but gently cleansed of mucus and debris by a cotton swab soaked in a mild alkaline solution. Next the cervix should be carefully observed, noting the exact extent of the apparently normal squamous epithelium of the portio vaginalis. Schiller solution (one part iodine, two parts potassium iodide, 300 parts water) should be generously applied to the cervix with a cotton swab. Those areas of APPARENTLY NORMAL squamous epithelium prior to the application of Schiller's solution but failing to take the stain are termed "Schiller positive" and should then be biopsied. Only about 5 per cent of these will be carcinoma in situ, the remainder leukoparakeratosis, all having the common denominator of lacking glycogen.

In addition to biopsy of all Schiller-positive areas and those suggesting invasive carcinoma, an endocervical curettage should be done to determine the presence and extent of the in situ process within the endocervical canal, since in the majority the lesion arises on the endocervical side of the squamocolumnar junction. In those cases of carcinoma in situ in which the portio appears completely normal and is Schiller negative, the lesion lies entirely within the endocervical canal. Such cases of carcinoma in situ confined to the endocervical canal are initially diagnosed by random biopsy, endocervical curettage, or by either of these techniques after a positive vaginal smear has been found.

Routine vaginal smears examined for exfoliated malignant cells are an important aid to diagnosis, but it has been found by Paul A. Younge, at the Free Hospital for Women, that the single most important diagnostic tool is the Schiller test. This, combined with biopsy, endocervical curettage, and the vaginal smear makes it very unlikely that the diagnosis of carcinoma in situ wil be missed.

Microscopically the histological criteria are those of morphological malignancy in any nonkeratinized squamous epithelium, with loss of normal stratification and cellular polarity. Nuclei are extremely pleomorphic and there is marked mitotic activity well above the basal layer. Only occasionally is there disturbance of keratinization (parakeratosis and hyperkeratosis) with the superimposed pattern of carcinoma in situ. This morphologically malignant squamous epithelium involves the surface of the cervix (Fig. 1) but may also prolapse or grow into gland lumina, destroying the columnar epithelium and sometimes filling the gland lumina (Figs. 2, 3, 4).

Although it cannot be definitely proved, it appears that carcinoma in situ is the preinvasive form of invasive carcinoma. Nor has it been proved that carcinoma in situ left alone without treatment will INEVITABLY proceed to invasive carcinoma. The following data, however, suggest that both these concepts are valid.

1. The true incidence of both lesions is similar, 0.034 per cent for carcinoma (Haagenson, quoted by Corscaden) and 0.053 per cent for carcinoma in situ (Scapier et al.).

2. Age distribution is more or less parallel, the in situ lesion appearing nine to

FIGURE 3. Higher-power detail of an area from the squamous-cell carcinoma in situ illustrated in Fig. 2. The carcinoma in situ will be noted projecting into the gland lumen. There is a moderate degree of pleomorphism and there are numerous mitoses. AFIP Acc. 321804. (×103.3.)

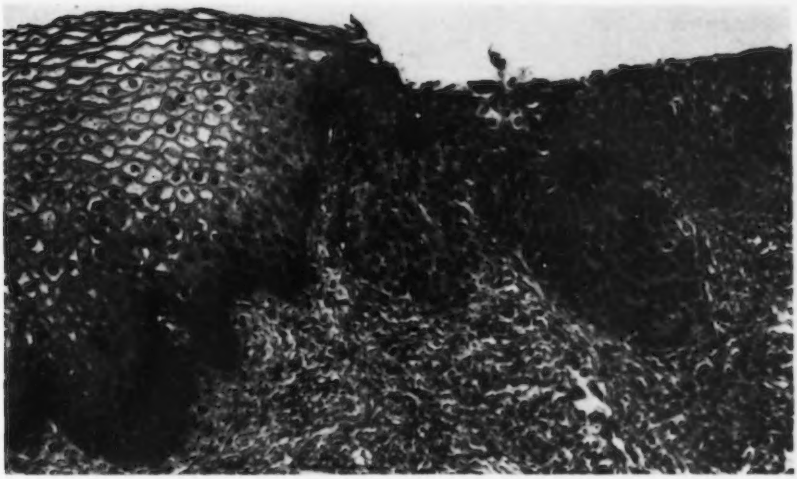


FIGURE 4. Squamous-cell carcinoma in situ of the cervix involving the surface only and continuous with squamous epithelium on the portio vaginalis. The carcinoma in situ, in which there is loss of polarity of cells and nuclear pleomorphism, may be contrasted with the normal stratified squamous epithelium on the left. AFIP Acc. 218754-194. (×130.5.)

ten years earlier than invasive cancer. The average age for the in situ lesion is 38 years and for clinically evident invasive carcinoma 51 years. Of interest is the fact that a large series of definite, but not clinically evident, cancers has an average age of 48.5 years.

3. The occurrence of both lesions is similar in ethnic or racial groups. Jewish women have only one fifth as much invasive cancer and one sixth as much carcinoma in situ as do non-Jewish women. Both carcinoma in situ and invasive cancer are twice as common in Negro as in white women.

4. Carcinoma in situ progressing to invasive carcinoma has been observed in a few cases. These are both retrospective and prospective in type, the former being much more numerous than the latter.

Retrospective cases are those in which the diagnosis of invasive carcinoma has been made, and, on looking back into the patient's past history, it is found that she has had previous cervical biopsies, at least one of them showing carcinoma in situ. About fifty such cases are in the literature. The only difficulty with such cases is that there is no proof that the patient did not have a small focus of invasive carcinoma at the time of the original biopsies. At the Johns Hopkins Hospital, in a series of 723 cases of cervical cancer, in situ and invasive, eleven of thirteen cervical biopsies and two of eight curettings taken one to seventeen years before the diagnosis of cervical cancer was made showed carcinoma in situ. Of these thirteen patients, ten had developed invasive cancer, while three still had an in situ lesion two to six years after the original biopsy.

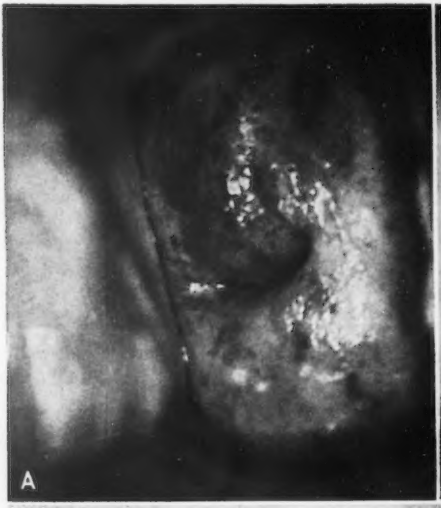
There are very few prospective cases, namely ones in which a diagnosis of carcinoma in situ has been made and the patient followed without further treatment. Such a group has been followed by Petersen in Denmark and 26 per cent found to develop invasive cancer in from five to twelve years.

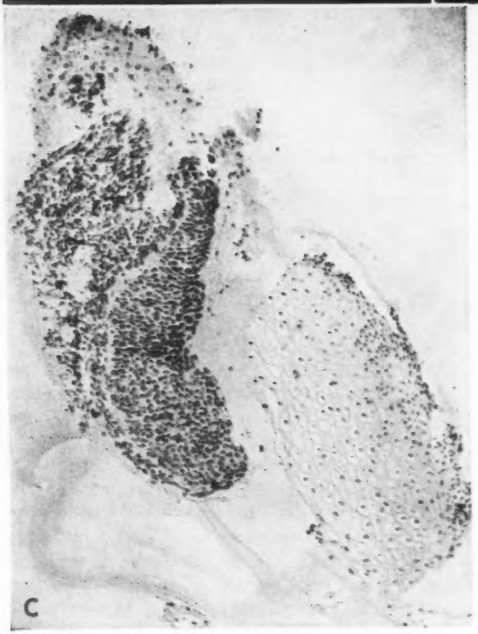
5. Apparent carcinoma in situ showing early invasion. If cases of apparent carcinoma in situ are examined further by semiserial sections very early invasion ("microcarcinoma") will be found in from 5 to 23 per cent. In such cases the

(Continued on page 202)

Diagnosis of Cervical Carcinoma in Situ

Courtesy of Dr. Arthur T. Hertig.

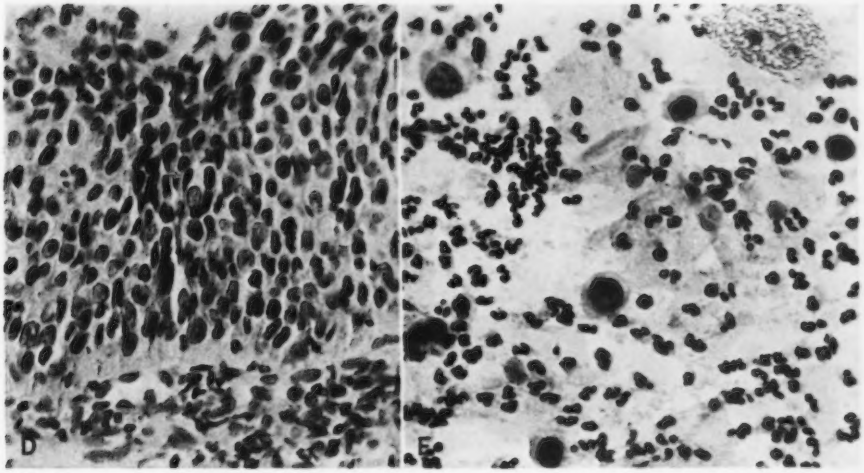




CASE 1. (F.H.W. U 34,770.) A, Squamous-cell carcinoma in situ of the cervix. The cervix after cleansing but prior to the application of Schiller's iodine. (F.H.W. S-47-4486.)

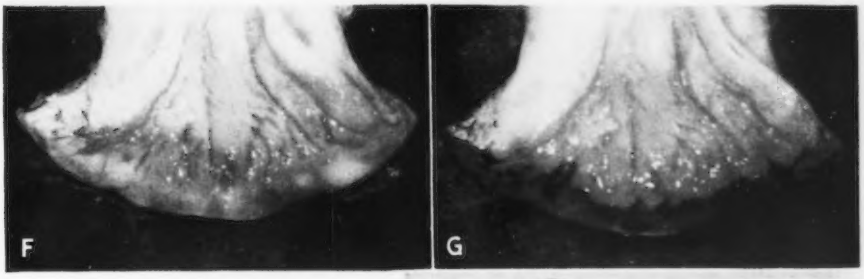
B. The cervix after application of Schiller's iodine. A large, irregularly shaped Schiller-positive area is seen on both anterior and posterior lips. The failure of this area to stain is in strong contrast with the mahogany brown of the rest of the cervix. (F.H.W. S-47-4486).

C. A small biopsy containing two short strips of squamous epithelium taken from the junction of the Schiller-positive area with the normal cervix. One of these is normal; with it the strip of malignant squamous epithelium (carcinoma in situ) may be contrasted. (F.H.W. S-47-3841. ×100.)



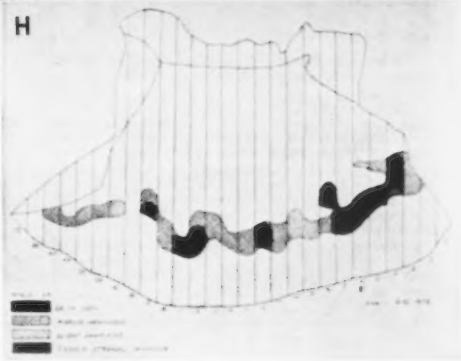
CASE 1. D, This high-power detail shows typical squamous-cell carcinoma in situ with loss of cellular polarity, nuclear pleomorphism, and numerous mitoses. (F.H.W. S-47-3841. ×400.)

E, Vaginal smear containing malignant cells with increased nuclear : cytoplasmic ratio, well-defined nuclear membrane, and nuclear hyperchromatism. The cytoplasm of these cells is well defined, a frequent finding in the malignant cells in the vaginal smear of patients with squamous-cell carcinoma in situ of the cervix. (F.H.W. VS-47-1595. × 400.)



CASE 2. (F.H.W. U 20,933; S-52-5172.)
F, A cervix amputated from a hysterectomy specimen and opened at 12 o'clock to show endocervix and squamocolumnar junction and apparently normal portio.

G, After application of Schiller's solution a Schiller-positive zone becomes apparent about the external os on the portio.



H, Graphic representation of the distribution of squamous-cell carcinoma in situ and varying degrees of anaplasia in this cervix. The vertical lines represent the serial blocks taken after fixation of the excised cervix.

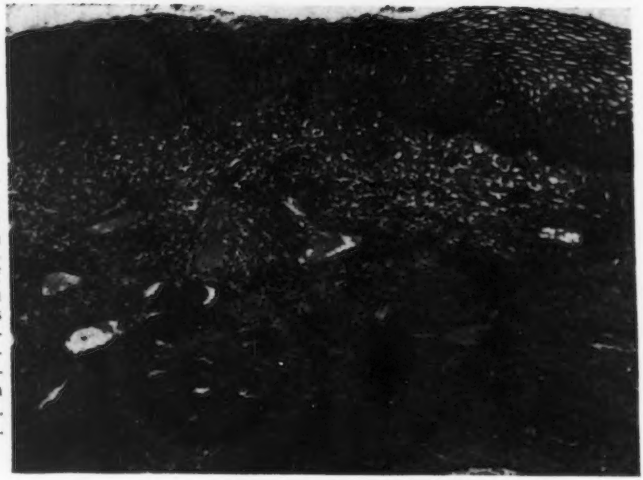


FIGURE 5. Invasive squamous-cell carcinoma of the cervix in which the in situ pattern is retained on the surface at the margin of the lesion. The surface epithelium on the left still retains the pattern of a carcinoma in situ but there are nests of invasive carcinoma in the underlying connective tissue and within a vascular channel. F.H.W. S-51-2841. (×60.)

microscopic stromal invasion is so early that these cases have the prognosis of an in situ carcinoma.

6. Invasive carcinoma still showing foci of the in situ pattern (Fig. 5). The presence of in situ carcinoma at the margin of a small invasive lesion suggests that the invasive carcinoma arose therefrom. As the lesion increases in size, it tends to obliterate this relationship.

7. Light-absorption data comparing carcinoma in situ and invasive carcinoma reported by Foraker confirm the observation of the pathologist who considers that carcinoma in situ LOOKS malignant.

8. Vaginal-smear correlation. Vaginal smears from patients with carcinoma in situ contain malignant cells in 70 to 82 per cent of cases, while 87 to 99 per cent of such smears from patients with invasive cancer contain malignant cells suggesting that carcinoma in situ is an early stage of invasive cancer. (The screening rate in unknown cases is about 70 per cent. The 82 per cent represents special search in known cases to see if even one malignant cell is present.)

In summary, carcinoma in situ is a morphological malignant alteration of the squamous epithelium at the junction of the portio vaginalis and endocervix (without stating the origin of that squamous epithelium) that usually precedes, occasionally is proved to give rise to, and is usually present in the vicinity of early intrauterine carcinoma.

References

1. *Corscaden, J. A.: Gynecologic Cancer, 2d ed. Baltimore. Williams and Wilkins Co. 1956.*

2. *Foraker, A. G.: Analysis of hyperchromatism in the histologic diagnosis of carcinoma of the cervix uteri; with special reference to intraepithelial and invasive squamous cell carcinoma and squamous metaplasia. A. M. A. Arch. Path. 53:250-256, 1952.*

3. *Hertig, A. T., and Mansell, H.: Tumors of the Female Sex Organs. Part 2. Vulva, Vagina and Uterus; Atlas of Tumor Pathology, Sect. IX, Fasc. 33. Washington, D. C. Armed Forces Institute of Pathology. In press.*

4. *Hertig, A. T., and Younge, P. A.: What is carcinoma in situ of the cervix? Is it the preinvasive form of true carcinoma? Am. J. Obst. & Gynec. 64:807-815; disc. 825-832, 1952.*

5. *Scapier, J.: Day, E., and Durfee, G. R.: Intraepithelial carcinoma of the cervix: a cytohistological and clinical study. Cancer 5:315-323, 1952.*

6. *Schiller, W.: Early diagnosis of carcinoma of the cervix. Surg., Gynec. & Obst. 56:210-222, 1933.*

7. *Stoddard, L. D.: The problem of carcinoma in situ with reference to the human cervix uteri. In McManus, J. F. A., Ed.: Progress in Fundamental Medicine. Philadelphia. Lea & Febiger. 1952; pp. 203-260.*

8. *Weiner, I.: Burke, L., and Goldberger, M. A.: Carcinoma of the cervix in Jewish women. Am. J. Obst. & Gynec. 61:418-422, 1951.*

9. *Younge, P. A.: A gynecologist's evaluation of methods of early cancer diagnosis. In Homburger, F., and Fishman, W. H., Eds.: The Laboratory Diagnosis of Cancer of the Cervix. New York. S. Karger. 1956; pp. 16-20; disc. 21-22.*

10. *Younge, P. A.: Hertig, A. T., and Armstrong, D.: A study of 135 cases of carcinoma in situ of the cervix at the Free Hospital for Women. Am. J. Obst. & Gynec. 58:867-892; disc. 892-895, 1949.*

Endometrial Biopsy

John C. Burch, M.D.

Endometrial biopsy can help to control cancer of the endometrium. No one, of course, can expect it to replace dilatation and curettage. However, with hospital costs what they are, it just is not feasible to put patients in the hospital to examine the endometrium unless the symptoms are suspicious of cancer. Since many patients with preinvasive and early invasive carcinoma do not present suspicious symptoms, many of these early cases remain undiagnosed. In order to find the early cases, endometrial studies are necessary in those patients with symptoms suggesting a benign lesion. Most of the time the differential diagnosis is between ovarian failure, uterine myoma, and early carcinoma of the endometrium. In such cases I use endometrial biopsy to sample the endometrium.

The technique of endometrial biopsy is applicable to most women. It can be carried out in the office and it is safe. If properly done, it is not too painful, and it usually produces a very satisfactory sample of the endometrium. To be sure, there are times when no tissue is obtained, but not infrequently there are "dry scrapes" with curettages.

In regard to endometrial biopsy, like everything else in medicine, there are conflicting opinions. The recent American Cancer Society monograph on *Cancer of the Female Genital Tract* by Herbert F. Traut and Ralph C. Benson has this to say:

"Curettage has the advantage of producing a tissue preparation that pathologists have been trained to evaluate. But it is expensive because to be done properly —that is, with sufficient thoroughness so that a negative report can be based upon adequate sampling — curettage requires hospitalization, anesthesia, and aseptic technique. As a result, it cannot be applied to the same patient yearly or semiannually. Office curettage and the suction curette should be completely abandoned by the profession as a means of determining the presence or absence of fundal cancer."

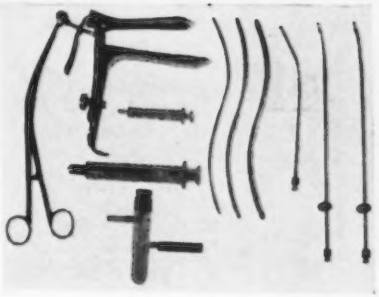


FIGURE 1. Instruments for endometrial biopsy.

John Wall and his associates at the M. D. Anderson Hospital come to a different conclusion. His material consisted of 445 women more than 35 years of age with irregular uterine bleeding. Adenocarcinoma of the endometrium was present in ninety-five of these, and the diagnosis was made by endometrial biopsy in ninety-two.

There have been many changes in the technique and apparatus, since Klingler and I first introduced endometrial biopsy by suction in 1932.[1, 2] Novak has added a great deal. He devised a good cannula, used mechanical suction, and emphasized a thorough sampling of the endometrium. He consistently advocated the procedure.

Suction makes it possible to use a small cannula and thus avoid dilating the cervix. If the cannula becomes stopped up, and it often does, suction fails to suck the endometrium into the cannula and results in inadequate sampling of the endometrium.

From Vanderbilt University Hospital, Louisville, Tennessee.

FIGURE 2. Endometrial biopsy by the suction technique.

For this reason, I check the patency of the cannula by bringing it out of the cervix two or three times in the course of covering the endometrial cavity. If air does not come through it, you know it is clogged.

I believe fear of hurting the patient causes many to do an incomplete job. Actually the pain is not too bad, if one can overcome the anxiety of the patient. It helps a lot to explain that the pain is crampy in nature and about as bad as a hard menstrual cramp. Because this is a familiar, and perhaps an often-experienced, sensation the prospect is not too frightening.

For years I used no anesthetic agent, but always I have been looking for one that was safe and practical. Recently I have used topical anesthesia with 1 per cent xylocaine. It seems to help, and certainly it is the best thing I have run across so far. A cotton-tipped applicator dipped in xylocaine serves admirably for anesthetizing the external cervix and the cervical canal. This topical anesthetization permits the cannula to pass through the open cervix with relatively little pain. If the cervix is closed, it allows the use of small Hegar dilators. It is rare that I find a cervix that I cannot dilate in the office. When the cannula passes the internal os, inject 3 to 5 cc. of xylocaine into the endometrial cavity without pressure. Then remove the syringe, letting the cavity drain for about five minutes. This allows ample time for the anesthesia to take effect. In obtaining the biopsy I go over the endometrial cavity at least twice using multiple, light, short strokes. Really it differs little from the conventional curettage, except in the use of the suction cannula instead of the curette. Most of the time the amount of tissue obtained compares favorably with that from curettage.

My apparatus is quite simple. I use the Randall suction cannula connected to a suction machine by pressure tubing. Between the cannula and the machine there is a trap for the collection of the specimen. If properly used, endometrial biopsy by suction can become an important and useful weapon in the attack on endometrial cancer. At the present time its extended use seems to offer much in controlling cancer of the endometrium.

References

1. *Burch, J. C., and Klingler, H. H.: Endometrial biopsy by suction. J. Tennessee M. A. 25:142, 1932.*

2. *Klingler, H. H., and Burch, J. C.: Suction in obtaining endometrial biopsies. J. A. M. A. 99:559-560, 1932.*

3. *Novak, E.: A suction-curet apparatus for endometrial biopsy. J. A. M. A. 104:1497-1498, 1935.*

4. *Traut, H. F., and Benson, R. C.: Cancer of the Female Genital Tract. New York, American Cancer Society, Inc., 1954.*

5. *Wall, J. A.; Fletcher, G. H., and MacDonald, E. J.: Endometrial biopsy as a standard diagnostic technique; a review of 445 cases. Am. J. Roentgenol. 71:95-101, 1954.*

Colposcopy and the Diagnosis of Early Carcinoma of the Uterine Cervix

Warren R. Lang, M.D.

Hinselmann, of Germany, the founder of colposcopy, wrote his first paper on the subject in 1925. Since that time, in some parts of the Western World but mainly in the German-speaking countries and in South America, the method has been used as a screening method for early cervical cancer.

Principles and Technique

Colposcopy may be defined as stereoscopic examination of the cervix under direct illumination. The usual magnification is about ×10 although enlargement to ×270 (colpomicroscopy) has been described. The ectocervix has received most attention by colposcopy, but the lower third of the endocervix, the vaginal epithelium, and the vulva, have also been studied by this method.

The findings of colposcopy depend in the main upon three characteristics of the cervical portio: epithelial configuration and architecture, epithelial thickness, and blood-vessel arrangement. The prime aim of colposcopy is to detect not only the preulcerative and preproliferative stages of invasive cancer but also the early atypical changes that may progress to carcinoma.

The instrument is binocular with a built-in light source. The headpiece is on an adjustable stand with a transformer in the base. Our own instrument, made by Moeller of Hamburg-Wedel, is similar to the one used by Hinselmann today. It magnifies ten or twenty times. The distance from the terminal lens to the object inspected is 22 cm. A built-in Leica attachment facilitates taking 35-mm. color transparencies for permanent records.

TABLE 1

Technique of Colposcopy

1. Insertion of speculum
2. Adjustment of colposcope
3. Inspection of cervix:
   (1). As is, *in situ*
   (2). After gentle cleansing
   (3). After application of 3% aqueous acetic acid
   (4). After aqueous iodine (Schiller test)
   (5). Change in magnification as desired

The conduct of a colposcopic examination is quite simple (Table 1). The patient is put in the lithotomy position and the cervix exposed. The colposcope is adjusted so that it looks at right angles onto the portio. Certain routine refinements, so-called "extended colposcopy" have been added, the two usual ones being swabbing of the cervix with 3 per cent aqueous acetic acid to increase clarity and aqueous iodine solution (Schiller test). Although many additional reagents have been suggested and tried, these two have stood the test of time. An average colposcopic examination, done carefully and exclusive of smear-taking and biopsy, should require only a few minutes.

Benign Findings

It is easy to differentiate squamous and columnar epithelium colposcopically; the former appears pinkish with fine white stippling, the latter "bubbly" and glistening. Three benign epithelial arrangements occur on the portio: (1) there may be only squamous epithelium; (2) there may be a rim of columnar epithelium around the os (ectopy); and (3) there may be an admixture of both squamous and columnar epithelium around the os (trans-

From the Department of Obstetrics and Gynecology, Jefferson Medical College, Philadelphia, Pennsylvania.

TABLE 2

Colposcopic Findings of Abnormal Cervical Epithelium Including Early Cervical Cancer

1. True leukoplakia
2. Ground leukoplakia
3. Mosaic leukoplakia
4. "Silent" iodine-negative areas
5. Uncharacteristic red areas
6. Adaptive vascular hypertrophy
7. Abnormal transformation zone
8. True erosion
9. Yellowish areas of proliferation

formation zone). The last mentioned is by far the most common finding in a woman of the childbearing age and is usually what is present when the woman is said to have a cervical "erosion."

Findings Suggestive of Atypism and Early Malignant Change

The changes seen colposcopically in cases of abnormal epithelium and cancer are listed in Table 2. By some writers, changes 1 through 4 are known as "simple atypical" changes and the remainder as "increased atypical" changes.

The term "leukoplakia" as used in colposcopic parlance has often been misunderstood. To the colposcopist, leukoplakia means, as the word does etymologically, a white patch. The area is white because the pink color of the underlying vascular stroma does not penetrate a thickened and/or keratinized epithelium. Three forms of leukoplakia are recognized: (1) TRUE LEUKOPLAKIA with keratosis and/or parakeratosis, (2) MOSAIC LEUKOPLAKIA, yellowish-white areas with a mosaic pattern, and (3) GROUND LEUKOPLAKIA, yellowish-white areas with a stippled appearance. The last two varieties are not recognizable as such by the naked eye. All varieties of leukoplakia are non–iodine staining. Areas of non–iodine staining in otherwise normal squamous epithelium, are spoken of as "silent" iodine-negative.

An increased vascularity, sometimes with irregularly distorted vessels (adaptive vascular hypertrophy) may be noted. At times there is an ABNORMAL TRANSFORMATION ZONE showing inflammatory changes and markedly leukoplakic rims around gland openings. True erosion with loss of surface epithelium and areas of proliferation are frequent in grossly evident cancer; these changes may be so minimal, however, that they are not evident except by colposcopy.

Colposcopy in Clinical Practice

We have been using the colposcope for approximately three years[4, 5] and have, to date, studied more than thirty new cases of cervical cancer and five cases of vulvar cancer in addition to examining many treated cases. Our purpose has not been to conduct a complete colposcopic screening program. Rather we have attempted to study cervixes that are clinically abnormal, those with abnormal smears, plus as many normal-appearing cervixes as possible. Papanicolaou smears have been done on all our colposcoped patients; biopsy, often with fractional curettage, has been carried out frequently. An example of colposcopic findings in an early cervical cancer is seen in Fig. 1.

We have been impressed by the occasional discovery of areas of abnormal epithelium when the portio demonstrates minimal deviation from the normal grossly and also by completely benign changes when speculum inspection in a good light would lead one to suspect early cancer. We have seen no instance of early portio cancer that did not demonstrate definite colposcopic abnormalities indicating biopsy. One can hazard an intelligent colposcopic "guess" about whether or not a given portio shows a benign or a malignant lesion, but biopsy is the final answer, just as it is for the abnormal cytological smear. An accurate history and a careful pelvic examination are not supplanted but merely supplemented by colposcopy.

There is no conflict between cytology and colposcopy.[2] The intent of each discipline is different. Cytology is a more diffuse screening method gathering its material from all areas of the genital tract, colposcopy a more localized one. With both methods, USED TOGETHER, it is in-

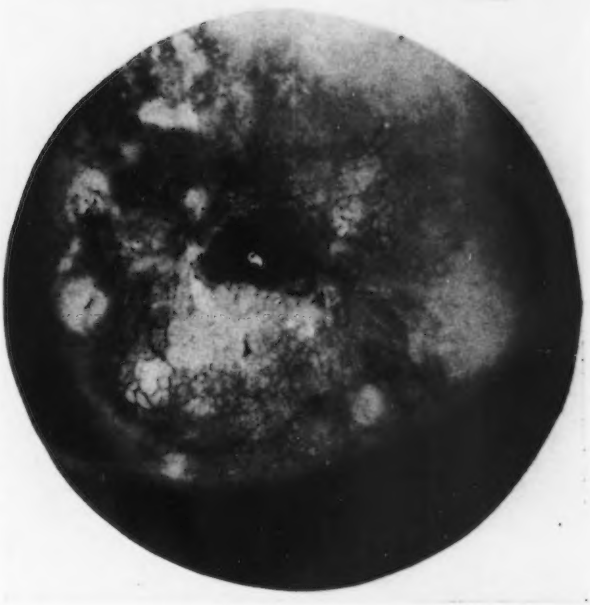


FIGURE 1. I.M., a 42-year-old Negress, gravida O, para O, had an early stage-1 carcinoma of the cervix that was asymptomatic. Colposcopic findings showed mosaic leukoplakia at 2 and 7 o'clock and true leukoplakia superior to ground leukoplakia at 11 o'clock. The slightly elevated area lateral to and below the area of ground leukoplakia showed adaptive vascular hypertrophy. Cytological smear was Papanicolaou Class III.

evitable that more early cancer will be detected.

A frequently voiced objection to colposcopy is that it is "not practical." This statement overlooks the fact that colposcopy is utilized abroad and is considered "practical" and of definite worth in detecting early abnormal changes. The instrument is expensive and special training is necessary for its intelligent use.

One of the principal advantages of colposcopy is that it leads to intensive inspection of the cervix—which is so often inspected carelessly. Then, too, the exact site of abnormal change can be determined and a directed biopsy performed, even during the examination itself. More selective biopsies are possible, resulting in a higher yield of cancer biopsies. The statistics of Mestwerdt are most impressive in this respect, since with the addition of colposcopy he was able to increase the percentage of positive biopsies more than twofold. Though difference of opinion exists, it would seem more rational to excise the entire area of atypical epithelium rather than taking only a sampling biopsy.

Summary

The principles, technique, and findings of colposcopy have been briefly presented. The colposcopic method is of distinct aid in cervical-cancer detection and in locating the exact site of biopsy. It deserves further trial in conjunction with measures currently in use.

References

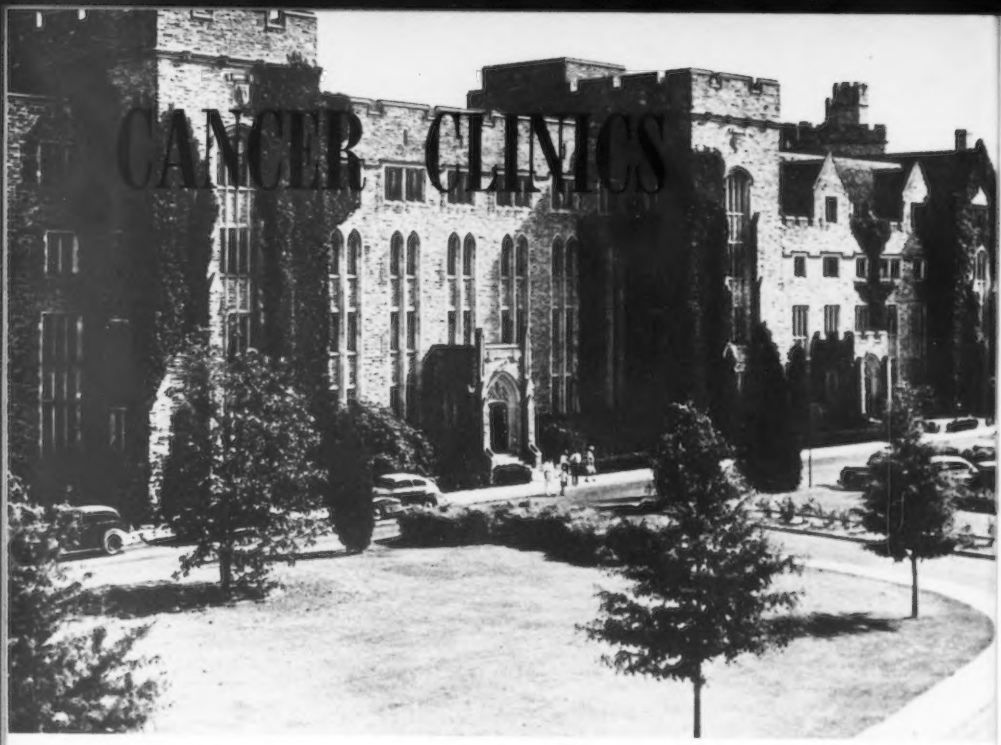
1. Hinselmann, H.: Verbesserung der Inspektionsmöglichkeiten von Vulva, Vagina und Portio. München. med. Wchnschr. 72:1733, 1925.

2. Lang, W. R., and Rakoff, A. E.: Colposcopy and cytology in the diagnosis of cervical atypism and cervical malignancy. Obst. & Gynec. (In press.)

3. Mestwerdt, G.: Atlas der Kolposkopie, 2d ed. Jena. Gustav Fischer, 1953.

4. Scheffey, L. C.: Bolten, K. A., and Lang, W. R.: Colposcopy: aid in diagnosis of cervical cancer. Obst. & Gynec. 5:294-306, 1955.

5. Scheffey, L. C.: Lang, W. R., and Tatarian, G.: An experimental program with colposcopy. Am. J. Obst. & Gynec. 70:876-886; disc. 886-888, 1955.



Stage-0 Carcinoma of the Cervix Uteri

A Conference in the Department of Obstetrics, Gynecology and Endocrinology, Duke University School of Medicine and Hospital

DR. CARTER: The purpose of this conference is to present the subject of stage-0 (intraepithelial) carcinoma of the cervix as we have seen it as a problem in the Department of Obstetrics, Gynecology and Endocrinology at Duke University Hospital from January 1, 1947, through June 30, 1956.

It must be stressed at the beginning of this discussion that this is a departmental problem and not one of a single individual. It should be stated also that we instituted this work for our own edification and education. It could not have advanced to its present status without the full cooperation of the Department of Pathology and other departments. These studies have engendered, therefore, a problem that has facets in several medical practices.

This is a study that includes dispensary and private patients who receive ambulatory care. Included also are ward and private patients who receive hospital care in the Department of Obstetrics, Gynecology and Endocrinology. The study represents, in addition, patients of colleagues and patients who are seen in consultation by our own staff members for other departments in the Hospital and Medical School.

We should like to emphasize our feeling that all females who enroll in our clinics, of whatever age, parity, or race, should have a systematized search for cancer and therefore should receive the benefits of routine screening by cytological techniques. It is important that obstetric and puerperal patients not be denied this screening procedure because our data show that stage-0 cancers occur

TABLE 1

Over-all Figures, January 1, 1947, to June 30, 1956

Total no., new patients	55,794
Total no., smear preparations	213,294
Approx. no., obst. patients	7,500
Approx. no., gynec. patients	48,294
Total no., stage-0 ca. cervix	308
Total no., squamous-cell ca. cervix	1,019

at the same rate in both obstetrical and gynecological patients. Exfoliative cytological techniques are essential for the frequent, early detection and subsequent diagnosis of stage-0 cancer of the cervix.

I would now ask the cytologist to present the material that constitutes this study.

DR. CUYLER: The pertinent data in the large amount of data collected can be presented best in tabular form (Tables 1, 2, 3, 4).

Table 1 shows that during the past nine and one-half years, 55,794 women were studied by means of genital cytological preparations. They represent approximately 7,500 obstetrical and 48,294 gynecological patients. The numbers of tumors shown do not represent necessarily the numbers that were seen in the Department during this period, but represent the numbers of patients with these lesions who had cytological studies. In this conference it should be understood that the term DIAGNOSIS signifies a pathologist's opinion that is based on the study of tissue sections. The term should not be confused with an interpretation resulting from studies in exfoliative cytology.

Table 2 lists the number of patients who had stage-0 and invasive carcinomas in the obstetrical group or gynecological group and by race. The incidences of the lesions are given.

Three hundred and eight of the 55,794 patients had diagnoses of stage-0 carcinoma, an incidence of 0.55 per cent. There were 232 white and seventy-six nonwhite patients. The predominance of white patients may be due in part to more regular, periodic examinations resulting from better education regarding cancer. This number is influenced also by the comparatively few private, nonwhite patients. Forty obstetrical patients had stage-0 carcinoma, an incidence of 0.53 per cent. Two hundred and sixty-eight gynecological patients had this lesion, an incidence of 0.55 per cent. These almost identical rates of occurrence are significant from the point of view of the controversial "lesion of pregnancy."

Squamous-cell carcinoma of the cervix was diagnosed in 1019 patients, an incidence of 1.82 per cent. There were 523 white and 496 nonwhite patients. Twenty-one of these cancers occurred in obstetrical patients, an incidence of 0.28 per cent. Nine hundred and ninety-eight gynecological patients had this cancer, an incidence of 2.06 per cent.

Table 3 lists the average ages of patients according to race and in the obstetrical and gynecological groups. The average age of patients who had stage-0 carcinoma of the cervix was 39.5 years; for white patients, 40.7 years; and for nonwhite patients, 37.5 years. The average age of patients who had squamous-cell carcinoma of the cervix was 48.8 years; of white patients, 49.2 years; and of nonwhite patients, 48.3 years. The difference between the average ages of those who had invasive cancer and stage-0 cancer is 9.3 years. This is pointed out for no other reason but to show that this figure closely corresponds to its counterpart in the data of other investigators.

Table 4 gives, in five-year age groups, the number of patients who had stage-0 carcinoma and the number of patients

TABLE 2

Stage-0 and Invasive Carcinoma of Cervix

	Obst.	Gynec.	Total
Stage-0 ca.	40	268	308
White	23	209	232
Nonwhite	17	59	76
Incidence	0.53%	0.55%	0.55%
Squamous-cell ca.	21	998	1019
White	9	514	523
Nonwhite	12	484	496
Incidence	0.28%	2.06%	1.82%

who had invasive squamous-cell cancer. There are several points of decided interest illustrated. Approximately one fifth (19.5 per cent) of those who had stage-0 cancer were less than 30 years of age. This group contains nulliparous married and single patients. In patients with squamous-cell carcinoma, but 4.6 per cent fall in the age range of less than 30 years of age. If we were to ascertain the upper limit of the age range of a group that would comprise a corresponding fifth of the 1019 patients who had invasive cancer, it would be found to be between the ages of 35 and 40 years. It will be remembered, incidentally, that the average age of the patients with stage-0 cancer was 39.5 years.

In further consideration of the stage-0 cancer patients, it is seen that 38.3 per cent were less than 35 years of age and that 36.3 per cent were in the fourth decade of life. If females, who comprise a group comparable to those reported here, sought the benefit of cytology techniques at clinics in which the lower age limit for this service was 40 years or 35 years, then 55.8 per cent or 38.3 per cent respectively would go undetected.

Table 2 shows that in obstetrical patients, the incidence of stage-0 carcinoma was 0.53 per cent, whereas the incidence of invasive carcinoma was 0.28 per cent. This difference may be related to the fact that, whereas 38.3 per cent of the patients with stage-0 cancer were less than 35 years of age, only 13.8 per cent of patients with invasive cancer fall in this age range.

The age range of patients with stage-0 cancer was from 19 to 80 years, and for squamous-cell cancer the range was from 21 to 85 years. If the figures for percentages of the total in this table were presented in graph form, it would be seen that the curves would be similar in shape but that the curve for stage-0 carcinoma would pass through age groups that are, in general, ten years younger than the corresponding figures in invasive cancer.

TABLE 3

Average Age in Carcinoma of the Cervix

	Obst.	Gynec.	Total
Stage-0 ca.	30.1	40.9	39.5
White	30.6	41.9	40.7
Nonwhite	29.3	37.5	37.5
Squamous-cell ca.	32.8	49.6	48.8
White	31.3	49.5	49.2
Nonwhite	33.8	48.6	48.3

TABLE 4

Comparison of the Incidence of Stage-0 and Invasive Carcinoma of the Cervix by Five-Year Age Groups

	Stage-0		Invasive	
Age, yr.	No. pt.	%	No. pt.	%
15–19	1	0.3	—	—
20–24	15	4.9	8	0.8
25–29	44	14.3	39	3.8
30–34	58	18.8	94	9.2
35–39	54	17.5	132	13.0
40–44	51	16.6	114	11.2
45–49	33	10.7	158	15.5
50–54	18	5.8	152	14.9
55–59	13	4.2	119	11.7
60–64	8	2.6	78	7.6
65–69	10	3.2	56	5.5
70–74	2	0.6	39	3.8
75–79	—	—	20	2.0
80–84	1	0.3	9	0.9
85–89	—	—	1	0.1
TOTAL	308		1,019	
Age range	19 to 80		21 to 85	

Seven of the 308 patients with stage-0 carcinoma had microscopic foci of invasion. One was an obstetrical patient. These patients have had definitive therapy; in five of them, the ovaries were not removed. To date there have been no cellular atypicalities in the genital smears of any of these seven patients.

DR. CARTER: Follow-up examinations cannot be overemphasized in any patient who has had a diagnosis of intraepithelial cervical carcinoma. Definitive treatment does not eradicate the problem of stage-0 carcinoma. If and when cellular atypias appear in smears from these patients, multiple-punch biopsies or even partial colpectomy must become a part of the follow-up examination. Obviously, it is mandatory to follow closely with cyto-

logical as well as pathological studies those patients who have not permitted definitive therapy.

DR. THOMAS: In our experience, the treatment of stage-0 cancer is highly individualized. Usually the procedure of choice is vaginal hysterectomy with conservation of the ovaries in the young patient. In spite of the fuller knowledge we will eventually have of this lesion, we believe that the marital status, age, and low parity will continue to be dominant factors in choosing the method of treatment. Clinical records of patients who illustrate points emphasized in this conference will now be presented.

Case 1

On November 20, 1950, a 22-year-old, colored, married woman, para 2-0-2, who desired more children presented herself at the out-patient clinic as an infertility problem. Genital smears made during the physical examination were thought to represent invasive squamous carcinoma. A repeat cytological study was thought to indicate intraepithelial carcinoma. Cold-knife conization was performed. The pathological diagnosis on the tissue thus obtained was intraepithelial carcinoma. All subsequent cytological studies failed to show atypical cells. As an endocrine patient, the patient became pregnant and was delivered on June 26, 1952. In April, 1954, she was delivered of her second baby. The pathological diagnosis on tissues removed by multiple-punch biopsy on October 20, 1955, was chronic cervicitis with epidermidalization. The last cytological study was made on April 23, 1956.

This was a co-operative patient who was cognizant of the cervical lesion. Since she was satisfied with the number of children she had, vaginal hysterectomy was performed on her request in October, 1955. The pathological diagnosis was: chronic cervicitis with epidermidalization; estrogenic endometrium.

The pertinent clinical history of this patient parallels the clinical courses of several young patients who had stage-0 carcinoma. They wanted more offspring.

Case 2

The following history illustrates the management of a middle-aged patient who has her family and who presents indications for vaginal hysterectomy other than intraepithelial carcinoma.

The patient, a 43-year-old, married, white woman, para 4-0-4, was seen first on April 14, 1955. The chief complaint was prolonged uterine bleeding. The clinical impression was prolapsus uteri and prolonged uterine bleeding, etiology unknown. Genital smears were interpreted as intraepithelial carcinoma. Repeat cytological preparations four days later were of no value for study. Concomitant cervical punch biopsy and curettage showed squamous metaplasia with atypias of the cervical epithelium and estrogenic endometrium. Cytological studies on May 5, 1955, showed marked epithelial atypicalities but did not show the criteria for carcinoma in situ. Smears made on May 23, 1955, again contained cytological evidence of intraepithelial carcinoma. Cold-knife conization of the cervix and curettage were performed on May 24, 1955. The pathological diagnosis on the tissue was intraepithelial carcinoma of the cervix and endometrial hyperplasia.

On July 14, 1955, vaginal hysterectomy, right oophorocystectomy, and anterior and posterior vaginal repair were performed. The pathological diagnosis was: chronic cystic cervicitis with squamous metaplasia; vaginal mucosa, no lesion; estrogenic endometrium; atrophic right ovary with follicular cyst.

No epithelial atypias have been seen in the smear preparations made since cervical conization. The last study was made on June 12, 1956.

Case 3

The following patient has a long-standing pathological diagnosis of intraepithelial carcinoma of the cervix but has not yet permitted definitive treatment.

The patient is a 31-year-old, colored, married woman, para 3-2-1, who came to the out-patient clinic on October 12, 1950,

for prenatal care. Cytological studies at this time indicated intraepithelial carcinoma of the cervix. Three subsequent cytological interpretations and two pathological studies of punch biopsies during this pregnancy indicated intraepithelial carcinoma of the cervix. The patient was delivered of a term infant on February 12, 1951. Intraepithelial carcinoma was diagnosed from cervical tissue obtained at the time of delivery. Cytological studies on April 9, 1951, showed intraepithelial carcinoma, and concomitant cervical biopsy material was diagnosed by the pathologist as intraepithelial carcinoma.

The patient returned on November 9, 1951, again pregnant. At this time, on a visit five weeks later, and on two dates in January, 1952, cytological studies indicated intraepithelial carcinoma. The patient aborted on February 17, 1952. Cytological and tissue studies were made of the cervix on April 10, 1952. The smears indicated intraepithelial carcinoma and the pathological diagnosis also was intraepithelial carcinoma.

Cold-knife conization of the cervix and curettage were performed on April 24, 1952. The pathological diagnosis was: early progestational endometrium; chronic cervicitis with squamous metaplasia and reserve-cell hyperplasia.

Smear preparations since cervical conization have not contained epithelial atypias. The last cytological study was made on February 2, 1953.

There was a pathological diagnosis of chronic cervicitis with endocervicitis on August 14, 1954, and one of chronic cystic cervicitis with epidermidalization and postabortal endometritis on June 23, 1956.

The patient had abortions in June, 1953; in September, 1955; and in June, 1956.

We realize that cytological studies are necessary in the detection of stage-0 carcinoma and are important in follow-up examinations of patients who have had this lesion. They are used, however, in a number of situations. Will the cytologist give briefly the uses of exfoliative cytology in our Department?

DR. CUYLER: The method is used primarily for the detection of cancer, intraepithelial carcinoma, and degrees of anaplasia that are less severe in character than those associated with the intraepithelial lesion. Estimation of estrogenic activity as judged by the vaginal epithelium is requested often as an aid in the clinical diagnoses of untimely ovarian failure; temporary absence of uterine bleeding; nonphysiological, Stein-Leventhal syndrome; inevitable abortion; premature climacteric changes; normal menarche; pregnancy; and increased estrogenic activity in postmenopausal patients. Exfoliative-cytology studies are used in following the progress of treated cancer patients and in the differential diagnosis of leukoplakic and simple inflammatory lesions of the cervix and vulva. Donovan bodies can be identified in properly prepared smears.

In regard to the lesion that is the subject of this conference, there are cell types, one in particular, in genital smears that for us identify with a certain degree of accuracy a lesion described as INTRAEPITHELIAL CARCINOMA. The cell type upon which we depend primarily is the malignant parabasal cell described by Papanicolaou. The accuracy of our interpretation is governed by histopathological diagnoses. Between 20 and 25 per cent of the pathologically diagnosed stage-0 carcinomas were interpreted as such from cytological studies. As a result of pathological diagnoses, we find that the cytological criteria we use for intraepithelial carcinoma are associated with lesions composed of marked atypias on the one hand or early invasive carcinoma on the other. Approximately 58 per cent of the pathologically diagnosed intraepithelial carcinomas were associated with cytological interpretations that mention this tumor. We believe, therefore, that our cytological criteria will identify early anaplasia. Approximately 25 per cent of these carcinomas in situ were thought by the cytologists to be invasive carcinomas. This is understandable when one considers the facts that intraepithelial carcinoma may arise as a well-differentiated tumor and that the limits of stage-0 carci-

noma must be established by histopathological studies. We have not been able to identify cytologically a cervical lesion that is said to be present in pregnancy and to regress following delivery. We have been able to recognize with some consistency, however, cellular abnormalities that are associated with *Trichomonas* infestation.

Dr. Fetter, our colleague in Clinical Pathology, now will present very briefly his concept of the lesion under discussion and his views on the place of exfoliative-cytology studies in this problem.

DR. FETTER: "Intraepithelial carcinoma of the cervix" is an unfortunate term, since it implies knowledge of the natural history of the lesion. Some of the patients with this lesion do develop invasive carcinoma, but the proof that the "intraepithelial" lesion becomes invasive is lacking. We have seen lesions that we have called "intraepithelial carcinoma with microscopic foci of invasion." In these cervixes invasive buds of epithelium extend through the epithelial basement membrane into the underlying tissues. Usually there is a chronic inflammatory reaction in these cervixes, and it may be that the agent evoking the reaction is responsible for the disruption of the basement membrane. It is difficult, however, to escape the impression that there is a real, and probably direct, relationship between "intraepithelial carcinoma" and some cases of invasive squamous-cell cervix carcinoma.

Cytological studies are extremely useful if properly interpreted. This interpretation must be made not only by the cytologist but by the clinician as well. By definition, the cytologist sees only exfoliated cells. The pathologist, on the other hand, sees all layers of the epithelium in addition to the underlying tissue. The pathologist is limited, however, by the fact that he usually receives small fragments of tissue from isolated areas, whereas the cytologist sees cells exfoliated from the entire cervix. A cytological examination should never be considered as diagnostic in the sense that definitive surgery is performed as a result of the report—histological confirmation of all diagnoses of carcinoma is necessary. For the purposes of screening a large group of patients, the cytological technique is invaluable.

DR. CARTER (in summary): As stated in this study, the diagnosis of stage-0 (intraepithelial) cancer of the cervix is not only a demanding departmental problem but must involve also the closest cooperation with other departments.

All females should have the advantages of screening and study by exfoliative-cytology techniques. Age, parity, or race should not be used to withhold the techniques from these patients in their clinical evaluation.

A review of any clinical material must emphasize that stage-0 cancer may be found in cervixes, and in cervical stumps, in which no clinical manifestations of the lesion are apparent to the examiner.

The pregnant patient, and those patients in the puerperium, should not be excluded from these studies.

Proper screening techniques, biopsy techniques and techniques for follow-up should be scrutinized with care, not only for those patients who are being followed "conservatively" on the basis of age and low parity, but also for those patients who have had definitive therapy.

The calculated risk assumed in following patients with the lesion in a conservative manner is equaled by that risk assumed in any definitive therapeutic approach for the lesion.

From our own experience we must accept the lesion in the obstetrical patients as identical with the lesion in the nonpregnant patients.

All arguments concerning the genesis of the lesion, its nature, and its potentialities must be repeated again and again. To the patient with the lesion, to the cytologist, to the obstetrician and gynecologist, and to the pathologist, knowledge of the lesion in time may be possible and treatment of the lesion may be properly evaluated from combined studies and follow-up programs.

new developments in cancer

In Search of a Disease . . .

A unique class of drugs is in search of a disease to cure. They are amino-acridines, which stain the DNA of cell nuclei with a bright fluorescence, particularly the nuclei of dividing cells. They have been used by the British as bacteriostatic, and by Germans as virostatic, agents. Peter P. H. DeBruyn of the University of Chicago has found that tiny hydrogen bombs (radioactive tritium) can be tucked neatly into each molecule; and these bombs will continue to go off for several hours after reaching the target nuclei—their range is so short that the explosions do not reach the cytoplasm of the cell. The drugs have failed to affect the course of several animal tumors. One curious characteristic, however, has been found—the dye does not go to normal nerve or brain. DeBruyn and Lorenzo Rodriguez now are wondering whether boron-impregnated acridines might not prove useful in slow neutron bombardment of brain tumors.

Antibody Specificity . . .

The difficult task of sharpening the specificity of antisera has moved forward another pace—David Pressman of Roswell Park Memorial Institute has increased the accuracy of anti-kidney antibodies fiftyfold. The antiserum was produced by injecting mouse kidney into rabbits. Antibodies then were withdrawn from the rabbits, labeled with radioactive iodine, and injected into mice. Antibody uptake by various organs then was counted. In early tests, Pressman produced antibodies, only 0.3 per cent of which went to the kidney. Now, however, the antibodies have been purified to the point where 15 per cent go to the kidney—the other 85 per cent are excreted after a brief and broad distribution throughout the mouse body.

Deadly Timetable . . .

University of Minnesota scientists have found that cancer adheres to a deadly timetable—in mice a critical five days is the difference between complete immunity to cancer and certain death. Carlos Martinez, J. Bradley Aust, and John J. Bittner have implanted breast cancers in mice tails. If they whacked off the tails about twelve days later, the mice became immune to second transplants of the same cancer. But if they waited seventeen days before cutting off the tails, the tumor killed the mice; it had metastasized. The scientists also found that it takes about twelve days for immunity to develop. If they cut off the tails before that time, a second transplant spread with devastating speed and killed the mice more rapidly than if they had not been sensitized.

to have a periodic sputum examination. He said the family physician is equipped to take specimens and send them on to cytology centers. He expressed the opinion that few patients would submit to periodic bronchoscopy, and that, while bronchial washings have some advantage over sputum tests, the latter would prove to be the most popular because of their simplicity. He described the rise in lung cancer as a "very grim picture" and cited Overholt (Boston) in declaring that early bronchogenic carcinoma is five times as curable as are symptomatic, long-suspected cancers.

Mass Screening: Erickson (Memphis) reported that more than four unsuspected cancers of the uterine cervix and corpus had been picked up among every thousand women screened in the Memphis area. So far, 120,000 women have been examined cytologically in this project.

Nieburgs (New York) told of a project, begun in 1951, to screen women in Floyd County, Georgia, for cervical cancer. The peak age brackets for in situ carcinoma were 41 to 50 and older than 61, and for invasive carcinoma, older than 60. Smears of 117 (or 0.66 per cent) of the 17,761 women examined were positive, and eighty-three of these so far have been confirmed by biopsy. Carcinoma in situ was unsuspected in 92 per cent, and invasive cancer was unsuspected in 35 per cent. A "do-it-yourself" kit, consisting of a nylon and cotton tampon, a slide container that automatically smears slides with the tampon, and a mailing envelope, and selling for fifteen cents, was used and returned by 2472 women. Of the ones returned, 28 per cent were unsatisfactory (they contained no endocervical material, although there was an abundance of vaginal squamous cells). Yet 6.2 per cent of these slides were positive.

Raskin and others (Chicago) described an exfoliative method of screening for cancer of the pancreas, one of the most difficult to detect of the malignant tumors. They stimulated the pancreas with intravenous secretin and lavaged the duodenum with saline solution and examined the latter also. In seventy-three cases of suspected cancer of the pancreas, bile ducts, gallbladder, or duodenum, fifteen were found positive for cancer by preoperative exfoliative cytology. Twelve turned out to be cancer of the pancreas, and three of the gallbladder, common bile duct, and duodenum. Among the six negatives, proved false at laparotomy, five cases turned out to be cancer of the pancreas and one of the duodenum. There were no false positives.

A high point of the Congress was the confirmation of the early work by the Grahams (Harvard and Mass. General) by a panel of international experts, including Glucksmann (Cambridge), Fennell (Pittsburgh), Kendall (Hartford), Nielsen (Copenhagen), and Kjellgren (Gothenberg). They found that radiation sensitivity of both normal and malignant uterine cervical cells afforded practical prognostic standards and could be used to advantage in selecting cases for either surgery or radiation. Munguia and Franco (Mexico City) also confirmed the Grahams's early findings that radioresistant tumors could be made radiosensitive to a considerable degree and that the prognosis improved with preirradiation administration of testosterone. Meanwhile the Grahams have projected their work far beyond these relatively basic observations. They are now concentrating on cytological evidence of host resistance to tumors and on efforts to enhance natural resistance by inoculating with tumor antigens and adjuvants and irradiating the vaccinated areas.

So far they have treated thirty-six patients with a variety of cancers in this manner, but, beyond observing some promising cellular changes, they find it too early to report on clinical results.

Carcinoma in Situ: Younge (Brookline, Mass.) presented a persuasive argument for ultraconservative treatment of carcinoma in situ, particularly in women of childbearing age. He pointed to statistical evidence that carcinoma in situ exists about eight to ten years before it becomes invasive. He reported the following results of conservative treatment (conization and cauterization) of seventy-three patients with carcinoma in situ, fifty-eight of them followed more than five years and twenty-six from ten to twenty years. Three died of intercurrent disease; only one developed invasive cancer, but she is living and free of disease eighteen years after treatment. Of thirty-seven patients who eventually had hysterectomy for various reasons, carcinoma in situ remained in only seventeen; thirty-four still have the uterus intact and are free of disease; fourteen have had a total of twenty-two living children. All are free of cancer. These were selected patients and comprise about one quarter of those treated for carcinoma in situ at the Free Hospital for Women. The rest are treated by a simple total hysterectomy, with preservation of ovarian function when indicated.

COMING MEDICAL MEETINGS

Date	Meeting	City	Place
1956			
Dec. 26-31	American Association for the Advancement of Science	New York City	Hotel Statler (Headquarters)
1957			
Jan. 10-12	Annual Cancer Seminar, Arizona Division, American Cancer Society (Approved for Credit by the Academy of General Practice)	Phoenix	Paradise Inn
April 8-12	American College of Physicians	Boston	
April 12-14	American Association for Cancer Research	Chicago	
April 14-20	American Society for Experimental Pathology	Chicago	
April 15-21	Pan-American Medical Association, Tenth Congress	Mexico City, D.F.	
April 25-29	Pan American Congress on Cancer Cytology	Miami Beach, Florida	Eden Roc Hotel
May 5-10	International Congress of Otolaryngology	Washington, D. C.	Hotel Statler
May 12-13	International Congress of International Society of Bronchoesophagology	Philadelphia	
May 14-17	International Cancer Campaign Symposium on Biochemistry of Cancer	London	
May 30-June 1	American Radium Society 39th Annual Meeting	Quebec, P.Q.	Chateau Frontenac
June 17-21	Canadian Medical Association 90th Annual Meeting	Edmonton, Alberta	
July 7-14	International Society of Clinical Pathology	Brussels	
July 9-12	International Society of Geographical Pathology	Paris	

324

PHOTOENGRAVINGS BY STERLING ENGRAVING COMPANY, NEW YORK, NEW YORK
PRINTED IN THE UNITED STATES BY PACE PRESS, INC., NEW YORK, NEW YORK